The Journal of Pediatrics

VOL. 49 OCTOBER, 1956 NO. 4

TREATMENT OF ERYTHROBLASTOSIS FETALIS, WITH SPECIAL REFERENCE TO SENSITIZATION TO Rh-Hr FACTORS OTHER THAN **Rh_0**

A. S. WIENER, M.D., I. B. WEXLER, M.D., AND G. J. BRANCATO, M.D.
BROOKLYN, N. Y.

IN A previous paper,[1] we presented a summary of our experiences with exchange transfusion in the treatment of erythroblastosis fetalis up to 1954. Up to that time, a number of modifications in the technique had been introduced, the most recent of which, namely, the use of partially concentrated blood, appeared to offer the best prognosis for the severely affected erythroblastotic infant. Since then, further experience with this modification has confirmed the original favorable impression, and in this paper we propose to present and discuss our more recent results.

The bulk of the cases which we have treated are classical examples caused by **Rh_0** sensitization.* With the passage of years, an increasing number of instances of **hr′** sensitization has been encountered,[2-7] which, with the possible exception of A-B-O sensitization, appears to be second in importance to **Rh_0** sensitization in the pathogenesis of erythroblastosis fetalis. We propose, therefore, also to present a few examples of erythroblastosis caused by **hr′** sensitization and to discuss the special problems related to its management.

From the Division of Immunohematology, Jewish Hospital of Brooklyn, and the Norwegian Hospital of Brooklyn.

*Bold face type is used to distinguish blood factors from agglutinogens (cf. Wiener[1a]).

Rh_0 SENSITIZATION

As pointed out in our previous report, our latest refinement has been the use of relatively fresh (one- to three-day-old) bank blood, which has been allowed to sediment. From this sedimented blood (originally a mixture of 500 ml. of blood and 120 ml. of ACD solution), the supernatant plasma is aspirated down to the 450 ml. mark so as to concentrate the blood partially (hematocrit approximately 0.5).

The cases are initially classified as to severity based upon the maternal antibody titer at term, or, if available, the average of the antibody titers determined throughout the pregnancy. After this initial classification, the results of tests carried out on the infant, namely, cord and capillary hemoglobin concentration, red cell coating test, icterus index, and erythroblast

count, together with clinical findings, are evaluated, either to confirm or to modify the impression of severity afforded by the antenatal antibody tests. The amount of concentrated blood used for the exchange transfusion varies with both the severity of the case and the size of the infant. Larger infants and more severely affected ones of any size receive two units (800 to 900 ml.) at the outset. Smaller and less severely affected infants receive one unit (400 to 450 ml.). If, despite the initial exchange transfusion, there is evidence of progressive disease, as indicated by a marked increase in bilirubinemia, and especially erythroblastemia and high reticulocytosis, a second exchange is carried out, generally after twenty-four to forty-eight hours. When the maternal antibody titers are low and the serological and clinical findings are minimal, treatment is withheld. However, if within the first twenty-four to forty-eight hours the infant exhibits manifest signs of disease, especially rapidly increasing jaundice, exchange transfusion is carried out.

Under this most recent regimen there occurred a total of 166 infants for whom the indication for exchange transfusion arose.* Among the 166 treated babies, there were two who died and three who survived but had neurological sequelae, an over-all "mortality" rate of only 2.4 ± 1.1 per cent. Among the last eighty-eight babies treated none has died, though one of the survivors has neurological sequelae. This single instance we ascribe to undertreatment, since, when severe jaundice developed after the exchange transfusion, we failed to repeat the procedure. It should be mentioned that in no case have we ever done more than two exchange transfusions on any infant. This is consistent with our concept that the aim of the exchange transfusion is to arrest the progress of the disease by removal of coated red cells. The lowering of the bilirubin concentration which occurs following exchange transfusion has two phases. There is an immediate drop in bilirubin concentration after the transfusion, but this is followed by a rise as more bilirubin diffuses into the blood stream from the tissues; then there is a second, permanent fall due to the arrest of the disease process, resulting from the exchange transfusion.

In Table I are summarized the results obtained in the treatment of a total of 377 erythroblastotic infants encountered during the past decade. In the data, there appears to be no appreciable improvement in the over-all mortality rate prior to the introduction of the latest refinement in the technique of exchange transfusion, namely, the use of partially concentrated blood. However, these data are misleading in their crude form and unfair to our earlier series of exchange transfusion, because they make no allowance for differences in the severity of the disease. When severe cases are analyzed, the improvement in the mortality rate is apparent in the earlier series as well. Similarly, the seemingly fair results in babies who received no treatment or only simple transfusion therapy is due to the dilution of this series by a large number of mildly affected babies. On the other

*Unfortunately, accurate figures are not available for this period as to the number of cases of Rh_o sensitization in which stillbirths occurred, or in which a normal Rh-negative baby was born, or where there was a live-born Rh-positive baby who presented such mild serological and clinical findings that no treatment was given.

hand, since our earlier methods of exchange transfusion were not entirely innocuous, some mildly affected babies had been subjected to a treatment which in itself carried with it some danger of embarrassing the circulation by the introduction of excessive amounts of diluted citrated blood. In our latest modification, in which the volume of blood injected is equal to the amount of blood withdrawn, circulatory overload is avoided, and the beneficial effects of treatment are evident even among the more mildly affected babies.

Table I. Comparison of Results of All Different Methods of Treatment of Erythroblastosis

	ALL CASES			INITIALLY SEVERE CASES ONLY		
TREATMENT	NO. OF CASES	DIED OR NEUROLOGICAL SEQUELAE	MORTALITY* ± P.E.† (PER CENT)	NO. OF CASES	DIED OR NEUROLOGICAL SEQUELAE	MORTALITY ± P.E. (PER CENT)
None	29	6	20.9 ± 5.1	9	5	55.5 ± 10.6
Simple transfusion	38	8	21.0 ± 4.4	19	8	42.1 ± 7.8
All previous methods of exchange	144	25	17.3 ± 2.1	101	20	19.8 ± 2.6
Present method	166	5	3.0 ± 0.9	131	5	3.8 ± 1.0

*Mortality includes babies who survived and had neurological sequelae, as well as those who died.

†P.E. = probable error.

SENSITIZATION TO hr'

Present-day routine antenatal management in regard to isoimmunization in pregnancy is designed to detect instances of **Rh_0** sensitization only.[8] Thus, all expectant mothers are tested and the serum of those found to be Rh negative is examined for the presence of Rh antibodies. This regimen is practicable but it fails to detect the rare but important cases of Rh-Hr sensitization where the expectant mother is Rh positive. The recent development[9, 10] of a simplified method of detecting Rh-Hr sensitization, involving the use of test cells treated with proteolytic enzymes (especially papain and ficin), has made it possible to devise a practicable screening procedure, which can be easily applied to all pregnant women, Rh positive as well as Rh negative.

At the Jewish Hospital of Brooklyn, a sample of blood is drawn from every patient on admission to the obstetrical service. Every morning the collected blood specimens are received at the Blood Transfusion Laboratory where the serums are tested against suspensions of papain-treated (or ficin-treated) cells of types Rh_1Rh_1, Rh_2, and rh, respectively. All cases in which clumping is observed in any or all of these three tests are called to the attention of the attending immunohematologist for further investigation. This procedure has proved of value for detecting not only instances of **Rh_0** sensitization which have been overlooked during the pregnancy, but also examples of sensitization to other Rh-Hr blood factors, notably **hr'**. In patients admitted to other services this test has served to anticipate and prevent transfusion reactions, and also to

uncover examples of autosensitization in unrecognized cases of disseminated lupus erythematosus and acquired hemolytic anemia. Adopting the suggestion made to him by one of us (A. S. W.), Dr. L. J. Unger[17, 18] has been doing similar screening tests for Rh-Hr sensitization on Rh-negative donors and also on all Rh-positive as well as on Rh-negative patients, both antenatally and before blood transfusion.

The following case demonstrates the value of the screening test for Rh-Hr antibodies, using ficinated test cells, in anticipating the occurrence of erythroblastosis fetalis caused by sensitization to the **hr′** factor.

CASE 1. *Erythroblastosis fetalis caused by* **hr′** *sensitization resulting from blood transfusion, successfully treated by exchange transfusion.*

Our attention was called to this case when the patient was admitted to the hospital for an operation on a Bartholin cyst abscess. Since all surgical cases admitted to the Jewish Hospital of Brooklyn are routinely blood grouped, a specimen of the patient's blood was sent to the laboratory. There she was found to be Rh positive, but in the routine screening test for abnormal antibodies against enzyme-treated group O cells, strong clumping was observed. The case was then called to the attention of one of us for further study. When preliminary tests indicated that the patient was type Rh_1Rh_1 and that her serum contained **hr′** antibodies, a more complete investigation was carried out.

According to the history, the patient had had only one pregnancy, which terminated with the birth of a female baby, who was then 5 months old and entirely normal. The patient had had a severe post-partum hemorrhage for which she was given a blood transfusion. Grouping and Rh-Hr tests on the family gave the following results: the patient's group was O MN Rh_1Rh_1; her husband's was A_2 N Rh_1Rh_2; the child's was O N Rh_1Rh_1. Thus every member of the family was Rh positive, but the patient and her daughter were both **hr′** negative, while the husband was **hr′** positive. Since the daughter is **hr′** negative, it is obvious that the mother's **hr′** sensitization was not due to the pregnancy, but to the transfusion she had received post partum. As shown in Table II, in September, 1952, when the **hr′** antibodies were first discovered in the patient's serum, the degree of sensitization was extreme, since the titers obtained were 180 units by the albumin-plasma conglutination method, 300 units by the antiglobulin method, and 550 units by the enzyme technique. The operation on the Bartholin cyst was uneventful and no blood transfusion was required.

The patient and her husband were informed of the findings and it was pointed out that, since the husband was heterozygous for the **hr′** factor, in future pregnancies there was a 50 per cent chance of having either an **hr′**-negative or an **hr′**-positive baby. If the baby proved to be **hr′** negative, the mother's **hr′** antibodies could not harm him; on the other hand, if the baby was **hr′** positive, there was hardly any doubt that he would be erythroblastotic. In fact, in view of the extreme degree of **hr′** sensitization, such an **hr′**-positive baby could well be stillborn.

Within less than three months the patient returned with the news that she was pregnant for the second time. A repeat **hr′** antibody test showed that there had been a substantial drop in antibody titer, which was more noticeable by the albumin-plasma conglutination and antiglobulin methods than by the enzyme technique (cf. Table II). Since the titers were still quite high, however, it was decided to carry out a therapeutic abortion. We were impelled to endorse the procedure despite the 50 per cent chance of having a normal baby, because of the hysterical behavior of the patient and

the possibility that the continuation of the pregnancy might bring about a mental breakdown.

The patient was seen again fourteen months later, at which time the **hr′** antibody titer was found to be very low, so that it was demonstrable clearly by the enzyme technique only, the titer being about 10 units (cf. Table II). One year later the patient became pregnant for the third time and **hr′** antibody titrations then showed no balance of the pregnancy. Since in our experience[11] a significant rise in titer during the pregnancy, such as this patient exhibited, invariably indicates a leakage of incompatible fetal blood into the maternal circulation, the obstetrician was advised that the patient was carrying an **hr′**-positive erythroblastotic baby. On this basis, about two weeks before term, labor was induced and the baby was delivered.

TABLE II. RESULTS OF TITRATIONS OF **hr′** ANTIBODY IN THE SERUM OF THE PATIENT IN CASE 1

TIME OF TEST	TITER (UNITS)* BY METHOD OF: AGGLUTINATION	ALBUMIN-PLASMA CONGLUTINATION	ANTIGLOBULIN	FICINATED CELLS	REMARKS
9/16/52 5 Mo. after birth of first baby and after blood transfusion	0	180	300	550	On admission to hospital for Bartholin cyst operation
12/9/52 (During second pregnancy)	0	16	44	200	Therapeutic abortion performed
2/4/53 Interim titer	0	1½	—	7½	
During third pregnancy					
4/23/54	0	2	0	12	E. D. C. 12/11/54
7/14/54	0	0	0	9	
8/19/54	0	0	0	5	
9/17/54	0	0	0	12	
(Average of above four titers)	0	½	0	9½	
10/15/54	0	16	2	68	
11/5/54	0	12	6	76	
11/12/54	0	—	22	148	
11/19/54	0	15	12	36	
11/26/54	0	17	14	81	Labor induced
Average of above five titers	0	15	9	82	
12/3/54	1½	56	88	176	

*Titer in units is the reciprocal of the highest dilution which gives a distinct (one plus) reaction.

significant further change in the titer. Periodic antibody titrations were carried out and for the first two trimesters of the pregnancy there was no change in titer, the average results being about 10 units by the enzyme technique, with little or no reaction by the albumin-plasma conglutination and antiglobulin methods. At this point there was an abrupt rise in titer, which was then maintained for the

At birth, the baby, a girl, appeared to be clinically normal. The blood grouping tests showed her to belong to group O, type Rh_1Rh_2, so that she was **hr′** positive as predicted. The icterus index of the cord serum was 18 units, which is just above the upper limits of normal. The blood count was within normal limits, with a hemoglobin concentration of 18.5 grams per cent; a red cell count of 7.3 million

per cubic millimeter and 10 per cent reticulocytes but no erythroblasts on the smear. As expected, the direct antiglobulin test was positive, the degree of coating of the baby's red cells being about 65 per cent. Free **hr′** antibodies were found in the cord serum, the titers being 2 units by the albumin-plasma conglutination method, doubtful by the antiglobulin method, and 12 units by the enzyme technique. Since, despite these impressive serological findings, there was little clinical evidence of disease, it was elected to treat the baby expectantly.

Within twelve hours manifest jaundice appeared and the icterus index had risen to 64 units. In view of the rapid rise in the icterus index, an exchange transfusion was carried out, using two-day-old blood of group O, type Rh_1Rh_1. This consisted of a mixture of 500 ml. of blood and 120 ml. of ACD solution, which had sedimented in the refrigerator. From this was removed 150 ml. of citrated plasma, reducing the volume to about 450 ml. (hematocrit 0.50). The exchange transfusion was carried out in the usual manner, using the radial artery-saphenous vein technique, the 450 ml. of blood being introduced while an equal volume was withdrawn. The subsequent course was essentially uneventful. The last sample drawn at the exchange transfusion showed an icterus index of 50 units, but the following morning the icterus index had risen to 96 units. The jaundice then rapidly subsided and completely disappeared by the fifth day, at which time the baby was discharged with her mother. No further transfusion therapy was necessary, and the baby's subsequent physical and mental development has been normal.

The most interesting findings in the case just described were the results of the antibody titrations. This case demonstrates that the presence of a very high antibody titer does not necessarily preclude the possibility of subsequent successful pregnancies with babies having the blood factor to which the mother is sensitized. The reason for this is that, with the passage of time, there is a tendency for the antibody titer to fall, so that after a sufficient interval of time the titer may be low enough to make it worth while to undertake another pregnancy. In the present case the antibody titer dropped precipitously from 550 units by the enzyme technique to about 10 units, within the short space of less than five months. This is a far more rapid drop in titer than we have ever observed in cases of $\mathbf{Rh_0}$ sensitization, where high titers have often persisted for many years.[13, 13a] If we assume that the half-life of **hr′** antibodies is about a month, as has been found for $\mathbf{Rh_0}$ antibodies in newborn Rh-negative babies,[12] then the drop in the **hr′** antibody titer in the present case is approximately what would be expected under the assumption that antibody production had almost completely ceased after the first test was done in September, 1952 (cf. Table II).

The value of the enzyme test is further exemplified by the fact that the **hr′** antibodies continued to be demonstrable in the patient's serum after the other methods gave negative results, just as in the cases of $\mathbf{Rh_0}$ sensitization.[13] This case also demonstrates the value of antibody titrations during pregnancy for predicting the Rh-Hr blood type of the unborn baby. When a rise in antibody titer was observed, we correctly predicted that the baby was **hr′** positive. We have never observed a significant (beyond the limits of error of the laboratory method) rise in antibody titer antenatally when the fetus lacked the blood factor to which the mother is sensitized. Thus,

our own experience contradicts many reports in the literature claiming so-called nonspecific, anamnestic rises in the titer of **Rh_0** antibodies in mothers carrying Rh-negative babies.[14]

CASE 2.—*Erythroblastosis fetalis caused by* **hr′** *sensitization, with a high titer of antibodies in the maternal serum, but clearly demonstrable only by the enzyme technique.*

The patient, a boy, was born after an uncomplicated pregnancy and delivered in August, 1953. His mother had never received a blood transfusion and had had only one previous pregnancy, which resulted in the birth of a full-term normal girl. Routine antenatal tests had established that the mother was Rh positive, group A.

When the newborn baby was 3 hours old, he was found to be jaundiced. The hemoglobin concentration was only 13 grams per cent, and the smear showed innumerable nucleated red cells. The baby's blood typed as group O, Rh positive, and the direct antiglobulin test for coating of the baby's cells was negative. However, when preliminary tests for abnormal antibodies on the mother's serum against enzyme-treated cells were positive, a tentative diagnosis of erythroblastosis fetalis was made, though it was evident that some antigen other than **Rh_0** was responsible. As a stopgap procedure, the baby was given a transfusion of 75 ml. of the mother's washed, packed, red cells.

Complete grouping tests were then carried out, with the results shown in Table III. As shown in the table, the mother is **hr′** negative, while the father and both children are **hr′** positive. Antibody tests showed the mother to be strongly sensitized to the **hr′** factor, but the **hr′** antibodies were clearly demonstrable only by the enzyme technique, as follows: agglutination method, negative; albumin-plasma conglutination method, positive, 3 units; antiglobulin method, negative; ficinated cells, positive, 192 units. Despite the fact that the baby's cells gave a negative direct antiglobulin reaction, his serum contained free **hr′** antibodies with a titer of 48 units for ficin-treated cells.

On the second day of life, the patient was found to be more deeply jaundiced and apathetic. The hemoglobin concentration had risen to 14.6 grams per cent, but the icterus index was 72 units. By the time arrangements for an exchange transfusion had been completed, the icterus index had risen further to 120 units. For the exchange transfusion, 430 ml. of partly concentrated (hematocrit 0.50) bank blood of type Rh_1Rh_1, group A, was used. The baby withstood the procedure well, and following the transfusion the jaundice rapidly subsided, so that by the fifth day he was no longer jaundiced. No further treatment was required and the baby's subsequent physical and mental development has been normal. A repeat antibody titration on the mother's serum one year later gave the following titers: agglutination method, negative; albumin-plasma conglutination method, positive, 4½ units; antiglobulin method, negative; and enzyme-treated cells, positive, 60 units.

The aspect of this case worthy of special comment is that, though the mother was strongly sensitized to the **hr′** factor, the antibodies failed to

TABLE III. GROUPING TESTS ON FAMILY OF CASE 2

BLOOD OF	A-B-O GROUP	M-N TYPE	KELL TYPE	Rh-Hr TYPE
Father	A_2	MN	k	rh
Mother	A_2	MN	K	Rh_1Rh_1
First child	O	M	k	Rh_1rh
Second child	O	MN	K	Rh_1rh

react by the antiglobulin method and were clearly demonstrable only by the enzyme technique. This peculiar behavior of the antibody accounts for the negative direct antiglobulin reaction on the baby's red cells. In our experience this form of antibody is common in cases of **hr′** sensitization, though it has also been encountered in **Rh_0** sensitization. Thus, there are at least two sharply defined forms of univalent Rh-Hr antibodies. One form is demonstrable by the albumin-plasma conglutination and the antiglobulin techniques as well as the enzyme technique, and when of high titer gives a positive blocking reaction; while the second form reacts distinctly only by the enzyme technique. The latter appears to be less lethal, but it has on at least one occasion in our experience been responsible for severe neurological sequelae. Moreover, we have encountered a number of obscure hemolytic transfusion reactions which could be resolved only by testing for isoantibodies by the enzyme technique, including a number of patients of type Rh_1 who had become sensitized to the **rh″** factor.

With regard to the prognosis in future pregnancies for the couple described here, since the father belongs to type rh, he is homozygous for the **hr′** factor, so that every future baby would have to be **hr′** positive. Therefore, so long as the mother's **hr′** antibody titer remains high, every baby born alive would probably have to be treated by exchange transfusion.

CASE 3.—*Fatal erythroblastosis fetalis caused by* **hr′** *sensitization, treated by late simple transfusion; kernicterus.*

Our attention was called to this patient, a baby boy, on the third day of life, at which time he was severely jaundiced and had hepatosplenomegaly and anemia. The following history was elicited. The mother, who was known to be Rh positive, had never received a blood transfusion, had had two previous pregnancies in 1937 and in 1942, respectively, which terminated with the birth of normal, full-term babies who are alive and well. The present pregnancy terminated on Dec. 5, 1952, with the birth of the patient at term. Delivery was complicated by the presence of two tight loops of cord about the neck, but apparently the baby sustained no harmful effects from this. At birth, the baby was said to have appeared to be slightly jaundiced, but otherwise was normal. On the second day of life jaundice became pronounced, and the hemoglobin concentration was found to be 12 grams per cent, with 10 nucleated red blood cells per 100 white blood cells on the blood smear. Since the mother was known to be Rh positive, the pediatrician did not consider the diagnosis of erythroblastosis at this time, but when on the third day of life the jaundice became intense we were called into consultation. A tentative diagnosis was made of erythroblastosis fetalis, caused by sensitization other than **Rh_0**, and an immediate transfusion of 60 ml. of the mother's washed red cells was given to the infant. Within twelve hours, however, the infant began to have respiratory distress, the temperature rose to 102° F., and the baby vomited all of his feedings. Jaundice was intense and the baby died shortly thereafter. Postmortem findings were those typical of erythroblastosis, with marked hepatosplenomegaly and nuclear jaundice.

Subsequent detailed grouping tests showed that the mother belonged to group $A_1Rh_1Rh_1$, while the baby belonged to group A_1Rh_1rh. The maternal serum contained **hr′** antibodies with the following titers: albumin-plasma technique, 34 units; antiglobulin technique, 42 units; ficinated cells, 128 units. The baby's cells gave a direct positive antiglobulin reaction.

the degree of coating being about 16 per cent. In addition, the baby's serum contained free **hr′** antibodies with the following titers: albumin-plasma conglutination, 5 units; anti-globulin technique, 8 units; ficinated cells, 52 units. Significantly, the blood obtained from the infant before the transfusion on the third day of life had an icterus index of 300 units (approximately equivalent to a bilirubin concentration of 50 mg. per cent.)

Unfortunately, this baby was born before the practice was instituted of performing routine enzyme tests for isoantibodies on all patients, both Rh positive and Rh negative. As a result, valuable time was lost before it was realized that the infant was erythroblastotic. When finally we were consulted, it was too late to carry out an exchange transfusion. There seems to be little doubt that had this baby been born after routine testing for antibodies had been instituted, the presence of **hr′** sensitization would have been detected at birth, exchange transfusion would have been carried out, and the baby could have been saved.

Inspection of Table III shows that erythroblastosis due to **hr′** sensitization is as serious a disease as that caused by **Rh_0** sensitization. Because the routine antenatal tests fail to detect **hr′** sensitization, in five of these cases the diagnosis was not made until clinical evidence of the disease was manifest. In one of these five cases death occurred before any treatment could be instituted, while the remaining four babies were treated by simple transfusion. Of the latter, one baby died, while of the three that survived one had severe neurological sequelae. On the other hand, in the other four cases of erythroblastosis caused by **hr′** sensitization, in which the diagnosis was made early and treatment by exchange transfusion was carried out, all four babies recovered promptly with no sequelae.

Thus, this small series of cases of erythroblastosis caused by sensitization to the **hr′** factor provides further testimony of the efficacy of exchange transfusion in the treatment of this disease. Although this form of erythroblastosis is much less common than that caused by **Rh_0** sensitization, when it does occur it appears to be just as serious. Therefore, it is recommended that provisions should be made in every hospital to institute testing procedures on all patients admitted in labor, so that instances of **hr′** sensitization can be recognized early and the appropriate treatment by exchange transfusion instituted promptly. In our hands, the most satisfactory screening test for this purpose is the testing of the maternal serum for its ability to clump ficin-treated group O cells of types Rh_1Rh_1, Rh_2, and rh. The direct antiglobulin test which might also be used as a screening test, for example, on all newborn bloods is not recommended for this purpose for the following reasons: (1) The test must be delayed until after the birth of the infant, when the cord blood becomes available, while blood for the enzyme test can be obtained from the mother at the time of admission to the hospital. (2) Routine direct antiglobulin tests are not practicable, because the test is tedious and subject to error, except in the hands of experts. On the other hand, the enzyme test is easy to perform and lends itself to routine application. (3) As has been pointed out, in many cases of **hr′** sensitization the antibodies react dis-

TABLE IV. LIST OF CASES OF hr′ SENSITIZATION

CASE NO.	METHOD OF SENSITIZATION	CLINICAL MANIFESTATIONS	REPRESENTATIVE ANTIBODY TITRATIONS				COMMENTS
			SALINE	ALBUMIN-PLASMA	ANTI-GLOBULIN	FICIN-ATED CELLS	
1.	Transfusion	Erythroblastosis fetalis	0	180	300	500	Successfuly treated by exchange transfusion (see detailed case report in text. For additional titers see Table II).
2.	Pregnancy	Erythroblastosis fetalis	0	4½	0	192	Successfully treated by exchange transfusion (see detailed case report in text).
3.	Pregnancy	Erythroblastosis fetalis	0	34	42	128	Treated by simple blood transfusion. Died third day; kernicterus (see detailed case report in text).
4.	Pregnancy	Erythroblastosis fetalis	0	12	9	208	Successfully treated by exchange transfusion.
5.	Pregnancy	Erythroblastosis fetalis	0	3	8	28	Successfully treated by exchange transfusion.
6.	Transfusion and pregnancy	Erythroblastosis fetalis	150	—§	—	—	Recovered after multiple simple transfusions.
7.*	Pregnancy	Erythroblastosis fetalis	0	16	—	192	Also sensitized to rh″ factor. Recovered after multiple simple transfusions.
8.†	Pregnancy	Erythroblastosis fetalis	0	10	—	—	Also sensitized to rh″ factor. Simple transfusion therapy. Baby survived but had severe neurological sequelae.
9.*	Transfusion (plasma?) and pregnancy	Erythroblastosis fetalis	0	5	—	—	Died before treatment could be started.
10.	Pregnancy	Erythroblastosis fetalis	0	6	3	20	Diagnosed antenatally. Successfully treated by exchange transfusion.
11.	Transfusion and pregnancy	Stillbirth (no autopsy)	0	1½	—	230	Mother had hydramnios.
12.	Transfusion and pregnancy		0	—	2	15	Post-partum titers.
13.	Not known	Studied because baby had A-B-O hemolytic disease. Mother and baby both type Rh_1Rh_1	0 0	6 7	— —	54 → Mother's titer. 65 → Baby's titer.	
14.	Transfusion	Hemolytic transfusion reaction	0	200	130	430	Recovered.
15.‡	Transfusion	Hemolytic transfusion reaction	0	—	32	190	Died.

TABLE IV.—CONT'D

CASE NO.	METHOD OF SENSITIZATION	CLINICAL MANIFESTATION	REPRESENTATIVE ANTIBODY TITRATIONS				COMMENTS
			SALINE	ALBUMIN-PLASMA	ANTI-GLOBULIN	FICIN-ATED CELLS	
16.	Transfusion	Hemolytic transfusion reaction	0	5	27	96	Also strongly sensitized to Kell factor. Recovered.
17.	Multiple plasma transfusions	Reactions to plasma transfusions	0	—	—	100	Transfusions of post-partum plasma were given for treatment of rheumatoid arthritis.
18.	Transfusion	Hemolytic transfusion reaction	0	½	½	140	Recovered.
19.	Transfusion	Hemolytic transfusion reaction	500	500	—	500	Patient had acquired hemolytic anemia. Splenectomy done. Recovered.
20.¶	Transfusion and pregnancy	Hemolytic transfusion reaction	250	250	—	—	Recovered. Patient's serum also contained cold anti-O agglutinins.
21.¶	Transfusion	Hemolytic transfusion reaction	4	—	—	—	Titrations were done after transfusion of 1,500 ml. of blood, all of which were hemolyzed. Died.

*Previously reported in detail (Wiener, A. S., and Brancato, G. J.: J. Lab. & Clin. Med. 46: 757, 1955).
†For detailed report see: Wiener, A. S., and Brancato, G. J.: Anesthesiology 9: 175, 1948.
‡Reported in full elsewhere (Wiener, A. S.: New York J. Med. 54: 3071, 1954).
¶For detailed report see: Wiener, A. S.: J. Lab. & Clin. Med. 33: 985, 1948.
§ = test not done.

tinctly only by the enzyme technique, so that the direct antiglobulin test for coating of the baby's cells may be negative. The danger of overlooking such cases does not exist when the enzyme screening test is carried out.

The enzyme test alone will not detect all cases of hemolytic disease. For example, Duffy and Kidd antigens are destroyed by treatment with enzyme, and can be detected only by the antiglobulin technique.[15, 16] Moreover, cases of A-B-O hemolytic disease are not detected by this enzyme test.

As shown in Table IV, **hr′** sensitization is also an important cause of serious hemolytic transfusion reactions. Out of six patients who had such hemolytic reactions two died, apparently as the result of the reactions. Thus, although **hr′** sensitization is a relatively rare complication in blood transfusion practice, when it does occur it is just as serious as $\mathbf{Rh_0}$ sensitization. In our experience, as a cause of intragroup hemolytic transfusion reactions **hr′** sensitization is second in frequency to $\mathbf{Rh_0}$ sensitization.

Until recently intragroup incompatibility caused by **hr′** sensitization was in many cases not demonstrable by in vitro tests in use, just as it was often impossible to demonstrate the presence of $\mathbf{Rh_0}$ sensitization in the days before tests for univalent Rh antibodies were developed. Thus, in 1948 a series of hemolytic transfusion reactions was reported by one of us[3] in which circumstantial evidence indicated that **hr′** sensitization was the cause of the reactions in most of the cases. Yet, in only a few cases was it possible at

that time to demonstrate the presence of **hr′** antibodies. Now, with the introduction of the enzyme test, it is possible to demonstrate the presence of **hr′** antibodies in every case. In our institution, the danger of intragroup transfusion reactions caused by **hr′** sensitization has virtually been eliminated by carrying out routine screening enzyme tests on all patients who are admitted to the surgical services, or who may require blood transfusions. As already mentioned, this test will detect not only $\mathbf{Rh_0}$ and **hr′** antibodies, but also other Rh-Hr antibodies.

SUMMARY

To date, 166 babies with erythroblastosis fetalis caused by $\mathbf{Rh_0}$ sensitization have been treated by our latest modification of exchange transfusion by the radial artery-saphenous vein technique. In this latest modification, partially concentrated blood (hematocrit 0.5), preferably not more than three days old, is used. This is prepared by removing part of the citrated plasma after sedimentation has occurred. Depending on the severity of the disease and the size of the baby, from 450 to 900 ml. of such concentrated blood is used for the transfusion. In severe cases the exchange transfusion is repeated. In no instance are more than two exchange transfusions deemed necessary. Among the 166 babies treated this way, only five babies died or had neurological sequelae, a crude mortality rate of only 3.0 ± 0.9 per cent. On the other hand, among babies treated by our earlier modifications, or by only simple transfusion, or receiving no treatment at all, the mortality rate ranged from 17 to 21 per cent. The difference in results is even more striking when the severity of the disease is taken into account. Thus, among severely affected babies who received no treatment the mortality rate was 65.5 ± 10.6 per cent; among those receiving simple transfusion therapy the mortality rate was 42.1 ± 7.8 per cent; among those treated by our previous methods of exchange transfusion the mortality rate was 19.8 ± 2.6; while among those treated by our latest modification of exchange transfusion, the mortality rate was only 3.8 ± 1.0 per cent.

The cases of erythroblastosis fetalis caused by sensitization to Rh-Hr factors other than $\mathbf{Rh_0}$ pose an important problem, since the routine antenatal screening test for $\mathbf{Rh_0}$ sensitization does not take them into account. Such cases are rare, but when they occur they are just as serious as instances of $\mathbf{Rh_0}$ sensitization. Thus, among nine cases of erythroblastosis fetalis caused by **hr′** sensitization, one baby died before treatment could be instituted. Of the remainder, four were treated by exchange transfusion and recovered uneventfully, while among the four treated by simple transfusion one died and one of the three who survived had severe neurological sequelae.

A simple screening test for $\mathbf{Rh_0}$ antibodies consists in testing the serum of the patient against ficin-treated cells of types Rh_1Rh_1, Rh_2, and rh, respectively. This test should be carried out on all patients in labor admitted to the obstetrical service, and on patients admitted to the surgical or other services, who might require blood transfusion therapy. Case histories are presented, which illustrate the value of this screening test. It is pointed out that in cases of **hr′** sensitization the antibodies, even when

present in high titer, may react only in tests against enzyme-treated cells and may fail to react in the conglutination and antiglobulin tests. This accounts for puzzling, severe cases of erythroblastosis fetalis in which the direct antiglobulin test for coating of the baby's red cells by Rh-Hr antibodies is negative. It is emphasized that certain antibodies, such as anti-**F** and anti-**J** are not detected by the enzyme test, so that the screening test against ficin-treated cells should supplement and not replace the other tests for isosensitization.

We wish to acknowledge our indebtedness to the Misses Ruth Henderson, Leona Rosen, Gloria Tulip, and Selma Vogel, who carried out the tests for antibodies for enzyme-treated cells in the Blood Transfusion Laboratory of the Jewish Hospital of Brooklyn. Their alertness in detecting unusual antibodies in the sera of women admitted in labor or in patients requiring blood transfusions can be credited with the saving of a number of lives.

REFERENCES

1. Wiener, A. S., Wexler, I. B., and Brancato, G. J.: Treatment of Erythroblastosis Fetalis by Exchange Transfusion, J. PEDIAT. **45**: 546, 1954.
1a. Wiener, A. S.: An Rh-Hr Syllabus, New York, 1954, Grune & Stratton.
2. Wiener, A. S., and Brancato, G. J.: Erythroblastosis Fetalis Caused by Double Sensitization to **rh″** and **hr′**, Anesthesiology **9**: 175, 1948.
3. Wiener, A. S.: Intragroup Incompatibility With Respect to the Hr Blood Factors as a Cause of "Minor" Hemolytic Transfusion Reaction, J. Lab. & Clin. Med. **33**: 985, 1948.
4. Sussman, L. N.: Sensitization to the Hr Factor by Blood Transfusion, Am. J. Clin. Path. **17**: 643, 1947.
5. Dunne, C. J., Jr., and Innella, Q. P.: Dual Sensitization to the **rh″** (E) and **hr′** (c) Factors Detected Antenatally, Blood **7**: 526, 1952.
6. Grundorfer, J.: Hemolytic Disease of the Newborn Infant Caused by Maternal Sensitization to the Blood Factor **hr′** (c), Blood **8**: 609, 1953.
7. Wiener, A. S., and Brancato, G. J.: Problems in the Management of Erythroblastosis Fetalis. II. Additional Examples Exhibiting Unusual Serological Findings, J. Lab. & Clin. Med. **46**: 757, 1955.
8. Wiener, A. S., and Wexler, I. B.: The Management of the Isosensitized Pregnant Patient and Her Erythroblastotic Infant, Med. Clin. North America **35**: 749, 1951.
9. Morton J. A., and Pickles, M. M.: Use of Trypsin in the Detection of Incomplete Antibodies, Nature (London) **159**: 779, 1947.
10. Wiener, A. S., and Katz, L.: Studies on the Use of Enzyme-Treated Red Cells in Tests for Rh Sensitization, J. Immunol. **66**: 215, 1951.
11. Wiener, A. S., Nappi, R., and Gordon E. B.: Studies in Rh Sensitization. II. Effect of Rh-Negative Pregnancies on Rh Antibody Titer, Blood **6**: 140, 1951.
12. Wiener, A. S.: The Half-Life of Passively Acquired Antibody Globulin Molecules in Infants, J. Exper. Med. **94**: 213, 1951.
13. Wiener, A. S., Nappi, R., and Gordon, E. B.: Studies in Rh Sensitization. IV. Persistence of Rh Antibodies in Serum of Sensitized Individuals, Blood **6**: 160, 1951.
13a. Brancato, G. J.: A Source of Error in the Antenatal Diagnosis of Erythroblastosis, Am. J. Obst. & Gynec. **69**: 882, 1955.
14. Wiener, A. S.: Misinformation Regarding Rh, J. A. M. A. **157**: 748, 1955.
15. Unger, L. J., and Katz, L.: The Effect of Trypsin on the Duffy Factor, J. Lab. & Clin. Med. **38**: 188, 1951.
16. Rosenfield, R. E., and Vogel, P.: The Identification of Hemagglutinins With Red Cells Altered With Trypsin, Tr. New York Acad. Sc. **13**: 213, 1951.
17. Unger, L. J.: Rh-Hr Factors and Their Specific Antibodies, as Applied to Blood Transfusion, Am. J. Clin. Path. **24**: 275, 1954.
18. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, ed. 5, St. Louis, 1956, The C. V. Mosby Co.

CORTISONE THERAPY OF LYE BURNS OF THE ESOPHAGUS

EDWARD S. RAY, M.D., AND DAVID L. MORGAN, M.D.
RICHMOND, VA.

ESOPHAGEAL stricture resulting from chemical burns of the esophagus is a distressing problem to manage and requires periodic bougienage for usually two years and sometimes longer. The ultimate goal is the prevention of such accidents through education and legislation. Since this accomplishment remains unattained at the present time, a search should continue for a form of therapy of the lye burn itself that will reduce the incidence of stricture formation, and at the same time be relatively safe to the patient.

Following the introduction of cortisone it was soon demonstrated[1, 2] in the experimental animal that this steroid had a potent inhibitory influence on the inflammatory response of tissue to injury. This inhibitory effect of cortisone on tissue response to injury and infection has been further demonstrated in its clinical use in human beings.

Rosenberg and associates[3] reported in 1951 that when large doses of cortisone were administered to rabbits after lye burns of the esophagus there was a remarkable decrease in the tendency to fibrous stricture formation. However, this antifibroblastic action of cortisone was accompanied by a high incidence of suppurative infections (usually of the thoracic cavity). Rosenberg and workers[4] then repeated these experiments with the administration of penicillin in addition to cortisone and reported their results in 1953. There was a very marked reduction in the suppurative infections that accompanied the lye burns of the esophagus when penicillin was given along with cortisone. However, of the twenty-one rabbits treated with cortisone and penicillin there were two that developed mediastinitis.

Weisskopf[5] carried out similar experiments on dogs and found that all untreated animals developed severe esophagitis and strictures. The treated animals were given Terramycin and cortisone, and none of these developed strictures. It is also important to note that none of the treated cases developed suppurative complications. In the same paper, Weisskopf reported a case of a 17-month-old child with the classical picture of a severe lye burn who was given cortisone 25 mg. and Terramycin 250 mg. every six hours for twelve days; a twelve-month follow-up of this patient revealed no evidence of stricture or any complication of the treatment.

Smith and associates[6] in 1953 reported a case of lye burn in which the patient was treated with cortisone, but the cortisone was not administered until the tenth day of the burn. A stricture developed in this case. The ineffectiveness of delayed cortisone ad-

From the Departments of Medicine and Pediatrics, Medical College of Virginia Hospital.

ministration to inhibit fibroblastic reaction of inflammatory tissue in experimental animals was demonstrated by the work of Spain and co-workers,[1] whose studies indicate that cortisone must be given within the first twenty-four or forty-eight hours following injury if it is to have an effective suppressive effect on the inflammatory response of injured tissue.

Because of these studies, we decided in 1954, to administer cortisone and antimicrobial drugs to consecutive patients with lye burns of the esophagus as they were admitted to our hospitals. We realized that there were potential dangers of serious mediastinal and pulmonary complications as a result of the use of cortisone in these cases, and because of this it was decided to hospitalize all patients throughout the period of cortisone administration. Because we have found it difficult to maintain adult patients with lye burns in the hospital longer than a few days, we have limited our evaluation of cortisone therapy to children.

MANAGEMENT OF LYE BURNS

This discussion of the handling of lye burns will be limited to such accidents as they occur in children. Since lye ingestion occurs primarily in children of the 1-to-4-year age group, the dosage of antimicrobial and steroid drugs will be for that age patient and must, of course, be modified for patients whose size and weight require a different dosage.

All children with lye burns are admitted to the pediatric service and are followed by this service and the medical chest service. The latter service carries out any endoscopy or bougienage that is required, but the responsibility of the patient rests with the department of pediatrics.

The question of gastric lavage is a controversial one, and although a few of our patients were so treated when they were admitted to the emergency room, we believe that it is safer not to pass a tube through the esophagus and certainly it is unwise to induce emesis in these cases. We favor the administration of olive oil and milk at frequent intervals to these patients.

Diet is limited to liquid foods for three days and then puréed foods during the first two weeks. The child is then placed on a general diet.

Antimicrobial drugs are given in all cases. Since the majority of these children have dysphagia either from pain or edema, it is necessary to give the drugs parenterally. We use either a combination of streptomycin (0.5 Gm. daily) and penicillin (1 million units daily) or one of the broad spectrum drugs, usually Terramycin (25 mg. per pound of body weight). These drugs are administered in divided doses at eight-hour intervals, and continued for several days after the steroid is discontinued. Our cases have been about equally divided between these two drug regimens and we have noted no difference.

Steroid Therapy.—Cortisone in doses of 25 mg. is given every six to eight hours, and initially this is given intramuscularly during the period of dysphagia, and then administered orally. Cortisone was continued for periods varying from seven to thirty days, which is indicative of the uncertainty of the optimum duration of steroid therapy in these cases. Recently we have been treating these patients for two weeks, after which the dosage is gradually reduced, and then

discontinued entirely after an additional week. ACTH is given for several days toward the end of steroid therapy to prepare the patient for the withdrawal of the cortisone.

In cases of severe burns the patient is induced to swallow a thread as soon as the initial dysphagia passes. This is done in order that bougienage may be readily carried out should a stricture develop. Bougienage can be safely performed over a previously swallowed thread. The thread is kept in place, and carried out through the nose in order to prevent the child from chewing the thread. The children usually tolerate the thread well, but occasionally their arms must be restrained for a few days. The swallowing of a silk thread should continue to be an important part of the management of these severe cases as it greatly facilitates the passage of dilating sounds in cases where stricture results. In our experience the only cases of stricture that requires esophageal resection are those where the obstruction has been complete, and the swallowing of a thread has been impossible.

All patients who suffer any dysphagia have esophagograms made prior to their discharge regardless of how completely their dysphagia has disappeared. These children are seen at two-week intervals following their discharge, and the parents are also instructed to bring the child back immediately if the child develops any difficulty in swallowing soft foods; this is in order to have the child swallow a thread before complete obstruction develops.

CLINICAL MATERIAL AND RESULTS

There have been eleven cases of lye burns in children admitted to our hospitals over the two-year period (1954 to 1956) that have received cortisone. All patients were from 1 to 4 years of age. Of this number, there were seven classed as severe burns as indicated by redness, edema, and excoriations of the lips, mouth, tongue, and pharynx; in addition, there was drooling of saliva and dysphagia present in these cases. Four cases were classed as mild burns with dysphagia. In two of the seven severely burned cases there was complete esophageal obstruction presumably due to acute inflammatory edema. One patient was unable to swallow for six days and the other for three days. In each of the seven severe cases, ability to swallow returned, and esophagograms prior to discharge revealed no demonstrable stricture.

Steroid therapy was started within twenty-four hours of the lye burn in ten cases and none of these patients developed an esophageal stricture. One child did not enter the hospital until the fourth day following the ingestion of lye at which time complete esophageal obstruction was present. After three days of steroid therapy, this patient was able to swallow liquids and at the end of ten days she was able to take a general diet and a barium swallow was normal. However, a stricture of the esophagus developed in this child three months later that has required bougienage. This experience is further evidence of the ineffectiveness of steroid when administration is delayed. As pointed out by Spain and associates,[1] the delay of several days in steroid therapy results in failure of this agent to effectively prevent formation of fibrous tissue following injury.

The ten patients who received immediate steroid therapy have shown no clinical evidence of stricture and have remained on a general diet since discharge from the hospital. Follow-up studies are from six months (the most recent case) to twenty-eight months (the first case); ten cases have now at least a nine-month follow-up. We have experienced no significant complication of cortisone therapy of lye burn when antimicrobial drugs are administered concurrently.

It was because of these encouraging results that we are recording our experience with cortisone treatment of lye burns. Our previous experience with lye burns has lead us to expect from 25 to 50 per cent of the patients to develop esophageal strictures.

SUMMARY

Eleven patients with cases of lye ingestion have been treated with cortisone and antimicrobial therapy. In one of these cases an esophageal stricture developed, but in this case therapy was not begun until the fourth day. No complication of cortisone therapy of acute lye burns was observed. Because of the limited number of patients treated, a final appraisal of this therapy of lye burn must await additional experience.

REFERENCES

1. Spain, D., Molomut, N., and Haber, A.: Biological Studies on Cortisone in Mice, Science **112:** 335, 1950.
2. Spain, D., Molomert, N., and Haber, A.: The Effect of Cortisone on the Formation of Granulation Tissue in Mice, Am. J. Path. **26:** 710, 1950.
3. Rosenberg, N., Kunderman, P. J., Vroman, L., and Moolten, S.: Prevention of Experimental Esophageal Stricture by Cortisone, Arch. Surg. **63:** 147, 1951.
4. Rosenberg, N., Kunderman, P. J., Vroman, L., and Moolten, S.: Prevention of Experimental Esophageal Stricture by Cortisone, Arch. Surg. **66:** 593, 1953.
5. Weisskopf, A.: Effects of Cortisone on Experimental Lye Burn of Esophagus, Ann. Otol., Rhin., & Laryng. **61:** 681, 1952.
6. Smith, V. M., Compton, R., Jr., and Palmer, E. D.: Cortisone and Acute Lye Corrosion of the Esophagus, Arch. Otolaryng. **58:** 235, 1953.

When the sensation of fear has been deeply engraven on the mind during infancy, it is seldom entirely eradicated in after life. It palsies, to a certain extent, the powers of reason, and produces, under particular circumstances, a deplorable state of mental imbecility; which not only detracts from the comfort of the individual, but lays him open to the inroads of disease. We are liable to be ruled often by the influence of incidents and impressions that we have forgotten; or, in other words, sensations are subject to be revived by association, when the causes which first produced them are remembered no longer. How studious, therefore, ought those who have the care of children to be, that no impressions be made on their minds, which, as Darwin has observed, may bias their affections, mislead their judgments, impair their coolness and firmness in situations of danger, or render nugatory their best resolves, to the end of their lives.

D. Francis Condie, on the Diseases of Children, 1871.

UNIVERSITY OF MICHIGAN LIBRARIES

RESERPINE IN CEREBRAL PALSY

RUSSELL D. HARRIS, M.D.,* OKLAHOMA CITY, OKLA., AND
ELIZABETH H. ROWLEY, R.N., NORMAN, OKLA.

THE effects of tension, emotional disturbance, and abnormal behavior patterns make the problem of treating children with cerebral palsy an extremely difficult one. This fact has been particularly apparent to us at our training center where youngsters with cerebral palsy are admitted for evaluation and physiotherapy.

Quite often therapy is delayed because the children require long periods of adjustment to their new environment, as it is difficult to achieve optimal results with these children unless they are sufficiently relaxed.

Many drugs have been used to facilitate or intensify the training of children with cerebral palsy, including Tolserol, Kused, Prostigmin, d-tubocurare, phenobarbital, Prenderol, alcohol, hyoscine, Menesia, and carbon dioxide. Some of these agents have been of value in specific cases but they all have limitations.

Upon learning of reserpine† and its ability to tranquilize without hypnosis, it was decided to evaluate this preparation in a few selected cases to determine its efficacy in cerebral palsy. Preliminary results were sufficiently promising to warrant continuation of this study.

PILOT STUDY

The initial study was on twenty-seven children ranging in age from 2 to 12 years, including cases of spasticity, rigidity, ataxia, and the following types of athetosis: tremor, deaf, tension, and nontension.

The initial dosage for the children from 3 to 12 years was 0.25 mg. reserpine, in the form of elixir, twice daily. The 2-year-old children were given 0.2 mg. once daily. All children were kept under close observation, and when tension was relieved, behavior patterns improved, emotions were controlled, or drowsiness appeared, the dosage was reduced by half or less. The group served as their own controls.

In order to estimate the duration of effects of reserpine, some dosages were discontinued after two or three weeks. Where no apparent clinical improvement was noted, the dosage was maintained for another six to eight weeks before discontinuance. After this preliminary testing, we felt we had gained sufficient experience with reserpine to estimate dosages for maximum therapeutic response.

CONTROL STUDY

Following this pilot study, we initiated a controlled evaluation of reserpine in patients with cerebral palsy. Forty-two children (including the initial twenty-seven) were divided into two groups. Group I was given 0.25 mg. reserpine (elixir Serpasil) daily. Group II was given placebos. The preparations were identical in color, taste, and all apparent characteristics. Only one person, the nursing supervisor, had knowledge of which prep-

From the Cerebral Palsy Institute, Norman, Okla.

*Address: McBride Clinic, Oklahoma City.

†Reserpine (Serpasil) for the study was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

aration was given. Group I received reserpine for a two-week period, following which they were changed to placebos and group II was then started on reserpine for a two-week period. The two groups were selected as nearly identical in diagnosis as possible. Distribution of the cases was as follows:

Athetosis	14	(aged 2,2,3,3,5,5,6,6,6,6, 7,8,11,11)
Spasticity	17	(aged 3,3,4,4,5,6,6,6,7,7,7, 10,11,11,12,14,17)
Ataxia	3	(aged 4,4,11)
Rigidity	3	(aged 3,5,10)
Mixed	5	(aged 5,5,6,7,9)
Total	42	

Observations noted as a result of medication were from an objective and subjective point of view. There was an unconscious (subjective) decrease in tension which facilitated therapy. As a result of this decrease in tension there was an objective observation by the therapists that treatment was more easily carried out. There was also an observable (objective) lessening of fear so that often the children would undertake a wider range of spontaneous activities such as standing-balance or ambulation with or without support.

The nursing personnel reported that all children on reserpine were happier and more cooperative and that there were fewer emotional upsets. In many instances the tension which these children developed was reduced so that they were better able to cooperate in the physiotherapy program. In some children where there had been fear of falling when walking, this fear was allayed and motivation for walking was gained. They tolerated their braces better and were able to manage them with greater ease. Children who were usually restless at night slept better and the usual sedation was lowered or completely withdrawn. There was an increase in appetite and many showed weight gains.

The occupational therapists found reserpine to be a valuable adjunct to the training program in releasing the extreme tensions and thereby facilitating exercises. They also found less motivation in the hyperkinetic athetoids because of lethargy in some cases, which was probably due to overdosage.

The Wechsler-Bellevue Form No. 1, Psychological Rating Test was used in evaluating these children, and no significant change was noted. However, better cooperation was achieved.

TABLE I. SUMMARY OF THE EFFECTS OF RESERPINE IN PATIENTS WITH CERTAIN CONDITIONS

DIAGNOSIS	IMPROVED	NOT IMPROVED	WORSE
Athetosis	9	4	1
Spasticity	7	10	0
Ataxia	2	1	0
Rigidity	2	1	0
Mixed types	2	3	0

No significant effect was recorded as a result of the placebo medications.

CASE REPORTS

Four unselected case histories follow:

CASE 1.—Patient aged 4 years, weight 41½ pounds. Diagnosis: spastic quadriplegia.

A placebo was given for two weeks, followed by 0.25 mg. reserpine daily for two weeks, and then 0.1 mg. reserpine daily for one week.

The patient was a Negro boy, unusually large for his age, with no speech involvement and only minimal involvement in his hands; his behavior pattern was characteristically one of cooperation and happiness. On Serpasil he remained alert and fun-loving, with no objective or subjective changes noted.

CASE 2.—Female, white, aged 6 years, weight 41 pounds. Diagnosis: tension athetoid.

A placebo was given for two weeks, followed by 0.25 mg. reserpine daily

UNIVERSITY OF MICHIGAN LIBRARIES

for two weeks, and then 0.1 mg. reserpine daily for two weeks.

This child showed such promising results on Serpasil that it was continued on a long-term basis. The child was usually prone to temper tantrums, considerable tension, and profuse perspiration. She became quiet and cooperative on Serpasil. No side effects of any kind were noted.

The speech therapist reported the child relaxed considerably on Serpasil. She attempted many words and frequently was successful and was more cooperative and interested in speech and training. No change was noted in physical therapy; however, this child had a subluxation of one hip, so that no ambulation was attempted. No change was noted in occupational therapy, but the child did very well in feeding herself considering the degree of her involvement.

CASE 3.—D. E., white male, aged 7 years, weight 31 pounds. Diagnosis: tension athetoid.

Reserpine 0.25 mg. daily was given for two weeks, followed by a placebo for two weeks, and 0.1 mg. reserpine daily for one week.

This boy was the picture of severe involvement, with no speech and no ability to feed himself, but was considered to be mentally alert. Since readmission he had shown very little improvement. On Serpasil medication he was quieter, less emotional, and gained weight because of improved appetite. In physical therapy he was more relaxed for table exercises, but was less active in the Hartwell carrier because of slower reactions. In occupational therapy his interest was improved but not the use of his hands. The speech therapist noted relaxation but no improvement in function on Serpasil medication.

CASE 4.—B. B., white male, aged 15 years, weight 85 pounds. Diagnosis: spastic quadriplegia.

Reserpine 0.25 mg. daily was given for two weeks, followed by a placebo daily for two weeks, and then 0.2 mg. reserpine daily for one week.

This boy was placid and slow moving but cooperative. Physical therapy staff reported that while he was on Serpasil medication his ability for self-help, as regard locking and unlocking his braces, improved but that his activity patterns otherwise remained static. His phobia of falling decreased while on the drug. No changes were noted in occupational therapy or speech programs.

UNTOWARD EFFECTS

There were no significant changes in blood pressure, although there was a slight reduction in cardiac rate. "Snuffy nose" was observed in some instances. There was one temporary case of urticaria noted in a 4-year-old child after three days on 0.2 mg. twice daily (pilot study) which cleared up promptly when reserpine was discontinued and did not return on resumption of medication of 0.1 mg. twice daily. Drowsiness was occasionally noted following release of tension, particularly with the larger doses of the drug. This was not felt to be a primary effect of reserpine but seemed to be merely secondary to the more general relaxed state present.

CONCLUSIONS

1. In our experience reserpine was a helpful adjunct in a training program for children with cerebral palsy. The drug produced better cooperation in all types of cases, replaced sedations, and served as a tranquilizer in emotional states.

2. Reserpine is especially beneficial in allaying tension in tension athetosis and in reduction of tremor in tremor athetoids.

3. Dosage must be individualized in each child.

4. Five minums (0.02 mg.) Serpasil elixir daily is adequate for maintenance therapy in small (25 to 30 pound) children.

ELECTROLYTE CONSIDERATIONS IN EXCHANGE TRANSFUSIONS FOR ERYTHROBLASTOSIS FETALIS

ROBERT P. BOLANDE, M.D., HOWARD S. TRAISMAN, M.D., AND
HERBERT F. PHILIPSBORN, JR., M.D.
CHICAGO, ILL.

ATTENTION has been focused on the serum electrolyte alterations that occur during exchange transfusions for erythroblastosis fetalis. Further interest in this has developed from an appreciation of the dramatic quantitative alterations which occur in plasma electrolytes of stored donor blood following refrigeration. A number of studies have stressed the nature and mechanism of these electrolyte alterations.[1-3] The plasma of stored, refrigerated blood shows a progressive increase in the concentration of potassium (K), as well as a diminution in the concentration of sodium. Such changes are due to the exchange of potassium and sodium across the red cell membrane. Under these circumstances there is a loss of potassium from the erythrocytes and it is replaced by sodium from the plasma. Prolonged cold storage of the erythrocyte impairs its glycolytic metabolism and engenders the above electrolyte changes. Normal metabolic activity of the cell membrane is necessary to maintain a high concentration of intracellular potassium, and to exclude sodium. This dynamic state requires the presence of ATP (adenosine triphosphate) and glucose. The metabolic activity of the refrigerated red cell's membrane may be restored by incubating it at 37° C. Under such circumstances potassium will re-enter the cell and sodium will be extruded.

Refrigerated blood used to replace the circulating blood of erythroblastotic infants is in many instances markedly hyperkalemic, and commonly hypocalcemic (citration effect). Under such circumstances it would seem reasonable to anticipate untoward physiologic effects and/or striking alterations in the serum electrolytes of the transfused infants. With this in mind, a study of serum electrolytes of twenty-three erythroblastotic infants both before and after twenty-six exchange transfusions was undertaken. The purpose was to see if there were a relationship between the babies' electrolytic pattern and clinical state.

METHOD OF STUDY

Twenty-three newborn infants, moderately to severely afflicted with erythroblastosis fetalis, were chosen for the study. These infants varied from 2 to 72 hours in age at the time of transfusion. Thirteen infants were male, and ten were female. Direct Coombs' tests were positive in all cases. A total of twenty-six replacement transfusions were performed, using 500 c.c. or less of compatible type O, Rh-negative blood. Each unit of blood

From the Otho S. A. Sprague Memorial Institute Laboratory and the Children's Memorial Hospital.

UNIVERSITY OF MICHIGAN LIBRARIES

was chosen from the blood bank without regard to duration of storage, although in no instance was it older than twenty-one days. Two patients (boy G and boy C) received repeat replacement transfusions within consecutive twenty-four-hour periods. All were transfused either by the umbilical vein or by a two-vessel technique. Twenty cubic centimeter aliquots of blood were used except where the infants were very ill, and then 10 c.c. aliquots were used. Ten per cent calcium gluconate was slowly injected after the administration of each 100 c.c. of blood. Venous blood samples were drawn at the beginning and end of the procedure. The blood samples were immediately centrifuged and the serum or plasma was removed for electrolyte determinations. Serum sodium and potassium were measured on the Weichselbaum flame photometer.

TABLE I

	PATIENT	K DONOR PLASMA	K BEFORE	K AFTER	Δ K	Na BEFORE	Na AFTER	Ca IV (C.C.)	RESULTS
I.	T. G.	4.80	5.45	4.89	−0.56	143.34	142.1	5	Survived
	J. W.	4.97	5.32	4.09	−1.23	146.5	141.6	5	Survived
	Girl C.	5.95	3.90	4.17	+0.27	151.3	144.95	6	Survived
	Boy G_1	6.0	4.2	4.10	−0.10	140.8	138.7	6	Progressive jaundice and anemia
	Boy G_2	7.4	4.3	5.2	+0.90	141.2	151.6	6	Progressive jaundice and anemia
	Boy G_3	3.1	--	7.8	--	139.5	143.8	6	Survived
II.	Boy M.	7.67	4.13	4.99	+0.86	144.0	144.0	6	Survived
	Girl E.	9.0	4.35	5.65	+1.30	148.7	145.7	10	Survived
	S. T.	9.2	4.08	4.55	+0.47	145.7	144.7	5	Survived
	R. G.	9.9	3.59	4.60	+1.01	149.2	147.6	5	Survived
	Girl W.	10.0	5.8	6.15	+0.35	138.1	137.98	6	Survived
	Boy P.	12.3	4.1	5.0	+0.09	142.4	145.3	6	Survived
	Girl C.	13.4	6.0	7.8	+1.08	160.8	176.0	6	Survived
	Boy B.	13.45	4.52	4.5	−0.02	147.6	144.7	6	Survived
	R. A.	19.7	5.5	4.29	−1.21	148.0	160.6	5	Survived
	Boy T.	13.4	6.3	6.38	+0.08	145.6	157.02	5	Survived
	Boy D.	16.7	4.05	4.33	+0.28	150.0	155.4	6	Survived
	Boy C_1	15.0	5.23	5.15	−0.08	139.4	156.5	6	Progressive jaundice and anemia
III.	Boy C_2	9.55	--	5.16	--	--	166.5	6	Cardiac arrest and resuscitated
	Boy D.	22.7	5.4	5.3	−0.1	146.1	146.1	6	Cardiac arrest and resuscitated
IV.	J. L.	17.4	4.59	4.23	−0.36	136.8	147.7	5	Died of ruptured spleen
	Girl J. W.	7.8	3.34	5.66	+2.32	140.8	142.6	7	Died with severe emphysema
V.	Girl V.	12.3	5.01	7.5	+2.49	150.96	148.6	6	Died after exchange
	Girl N.	21.1	3.95	6.55	+2.60	142.0	154.0	6	Died during exchange
	Boy D.	12.2	5.23	17.0	+11.70	142.1	177.6	6	Died 28 hr. after exchange
	T. K.	20.5	3.75	7.75	+4.00	143.3	141.3	0	Died during exchange

RESULTS

In Table I, the cases are arranged in five groups and in each instance the electrolyte determinations before and after the procedures are recorded. *Group I* consists of six patients receiving relatively normokalemic donor

blood (3.1 to 7.4 meq. per liter). All of these infants responded well following exchange transfusions. *Group II* is comprised of twelve patients receiving hyperkalemic blood (7.67 to 19.7 meq. per liter). All of these infants responded well to the exchange transfusion. *Group III* consists of two infants who received hyperkalemic blood and experienced cardiac arrest during the course of the procedure. Both were immediately resuscitated, the exchange transfusion completed, and the infants responded well. In *Group IV* are two patients who received hyperkalemic blood and died during the exchange transfusion. One of these infants died from a ruptured spleen,[4] and the other with severe pulmonary emphysema. From available clinical and pathologic evidence, it is thought that the deaths cannot be directly related to the exchange transfusion. *Group V* is comprised of four patients dying during or shortly after an exchange transfusion. In these infants death was thought to be directly related to the exchange transfusion. All of these erythroblastotic infants received hyperkalemic donor blood.

In Table II, the differences in serum potassium before and after the replacement transfusions is recorded as Δ K. The rate of potassium infusion expressed in milliequivalents per minute is listed as Rate_K. This value was calculated as follows:

$$\frac{(\text{Serum concentration K donor blood}) \times (\text{c.c. blood used}) \times (100 - \text{Hct.}) \times 10^{-3}}{\text{time of procedure (min.)}/2^*}$$

or,

$$\frac{(\text{Concentration K}) \times (\text{c.c. blood used}) \times 1.10 \times 10^{-3}}{\text{time (min.)}}$$

In all groups studied, the changes in sodium concentration were variable. These changes were not interpreted as being significant. Calcium determinations were not made; however, it was thought that the ionic factor was probably relatively constant, since all donor blood was citrated in a standard manner and approximately the same amount of calcium gluconate was infused in each instance.

Potassium was therefore the major consideration of this study. Four babies who received six replacement transfusions of normokalemic blood (Group I) all survived and did well. The remaining nineteen babies received twenty replacement transfusions of hyperkalemic blood. Among them, six deaths occurred. Twelve infants in Group II or Group III recovered from their hyperkalemic replacement transfusions without manifest untoward effects. Two cases of cardiac arrest occurred among the preceding twelve infants. In both instances, the infants were resuscitated and did well following the completion of their exchange transfusions.

Serum potassium levels showed a wide range in the surviving groups. However, most patients showed little or no significant Δ K. No correlation of patient serum K following exchange transfusion and the potassium concentration of donor plasma could be drawn. Some extremely hyperkalemic replacement transfusions were associ-

*The time of transfusion is halved, since only half the time of transfusion is devoted to the infusion of blood, while during the remaining time blood is withdrawn. The hematocrit (Hct) in most instances would be about 45 per cent, as only normal individuals were used as donors. We recognize that this formula is but a crude way of expressing mathematically a biological situation; nonetheless, we feel that the formula is sufficiently accurate for the purposes of the paper.

UNIVERSITY OF MICHIGAN LIBRARIES

ated with only slight elevations of patient serum potassium or even a diminution (R. A., and boy T). On the other hand, several slightly hyperkalemic donor bloods were associated with striking elevations in patient serum K (girl E and girl J. W.). Group V stands apart from the others in that all received markedly hyperkalemic blood and all showed Δ K values of the highest order.

blood without calcium supplement. Here the rate of K infusion was the highest encountered (0.360 meq. per minute), and the Δ K was also quite high. All babies weighed approximately 3,500 grams; therefore the factor of potassium dilution is of little significance in comparing Δ K among these infants.

TABLE II

	PATIENT	VOL. BLOOD (C.C.)	TIME OF TRANSFUSION (MINUTES)	Δ K	$RATE_K$ (MEQ./MIN.)
I.	T. G.	460	80	−0.56	0.030
	J. W.	460	72	−1.23	0.035
	Girl C.	500	80	+0.27	0.041
	Boy $G._1$	500	60	−0.10	0.055
	Boy $G._2$	500	67	+0.90	0.063
	Boy $G._3$	500	120	--	0.014
II.	Boy M.	500	50	+0.86	0.084
	Girl E.	500	75	+1.30	0.066
	S. T.	500	68	+0.47	0.074
	R. G.	500	75	+1.01	0.073
	Girl W.	500	75	+0.35	0.073
	Boy P.	500	120	+0.90	0.056
	Girl C.	500	70	+1.80	0.105
	Boy B.	500	65	−0.02	0.114
	R. A.	500	80	+1.21	0.135
	Boy T.	500	80	+0.08	0.092
	Boy D.	500	75	+0.28	0.123
	Boy $C._1$	500	63	−0.08	0.131
III.	Boy $C._2$	500	78	--	0.067
	Boy D.	485	90	−0.1	0.135
IV.	J. L.	500	107	−0.36	0.089
	Girl J. W.	500	64	+2.32	0.067
V.	Girl V.	500	80	+2.49	0.085
	Girl N.	500	90	+2.60	0.129
	Boy D.	455	47	+11.70	0.130
	T. K.	320	20	+4.0	0.360

The rate of potassium infusion was related to the content of K in donor plasma, in that roughly the same volume of blood was infused in the same time in most cases. Despite considerable overlap, the values in Group V were of a higher order than in all other groups. Patient T. K. of the latter group was of particular interest, in that the patient died during a rapid infusion of 320 c.c. of hyperkalemic

DISCUSSION

Miller and associates[5, 6] studied serum electrolyte changes in eight erythroblastotic infants during exchange transfusion. Measurements of the serum sodium and potassium concentrations at 100 c.c. intervals revealed hyperpotassemia in three out of five patients receiving older, hyperpotassemic donor blood. No significant deviations of serum potassium were present in the four remaining patients

receiving normokalemic blood. No clinical signs of potassium intoxication were evident.

In our study, the majority of patients appeared capable of handling rather large loads of infused potassium without serious changes in clinical status or serum K. The four babies whose deaths were believed to be related to their transfusions had high rates of K infusion and marked elevations of serum K following the procedure. Whether these elevations in serum K are physiologically significant cannot be stated, inasmuch as wide variations of serum K of newborn infants may occur normally. Physiologic interpretations based on K determination alone may be precarious.[7]

Since approximately one and one-half to two times the infant's blood volume is replaced in a routine exchange transfusion, it would seem that the serum of the patient at the conclusion of the procedure should rather closely approximate that of the donor blood. However, in the majority of the babies receiving hyperkalemic donor blood, the K value in the patient's serum was usually lower than that of the donor blood, at the termination of the procedure. This would indicate that the potassium ion rapidly leaves the blood vascular space. Whether this is accomplished by the kidneys or by diffusion into tissue spaces is not known.[6] Renal clearance would seem the less likely, considering that shock and parenchymal immaturity commonly are present in newborn erythroblastotic infants. In either case, the rate of K infusion would appear to be a critical factor. The high rates of K infusion observed in the four patients dying of exchange transfusions may be of importance in this regard. Whether the differences in infusion rate, between dying and surviving babies, are significant cannot be statistically determined because of the small number of infants studied. Another variable tending to complicate the picture is the progressive diminution in donor blood K occurring, to a variable degree, as the blood warms to room temperature during the course of the procedure. This variable was not taken into account in the calculations of rate. However, among the cases in which the potassium level of the donor's blood was studied before and after the transfusion, there was only slight diminution of plasma K.

It is of great importance to stress that, even in the majority of the severely diseased erythroblastotic infants studied, an impressive degree of physiologic resiliency was present. This allowed the infants to deal successfully with large infusions of ionically unphysiologic fluid. In this regard, Graham and Heyn[8] found that four erythroblastotic infants were able to maintain normal acid-base balance during exchange transfusions with unphysiologic blood.

SUMMARY AND CONCLUSIONS

1. Twenty-six exchange transfusions among twenty-three cases of erythroblastosis fetalis were studied for changes in serum electrolytes before and after the procedure. Particular attention was paid to potassium.

2. Many of the infants received donor blood which was markedly hyperkalemic.

UNIVERSITY OF MICHIGAN LIBRARIES

3. The majority of infants were capable of handling an abnormal load of infused potassium without untoward physiologic effects, or significant change in their serum potassium concentrations.

4. In some instances, rapid infusion of hyperkalemic donor blood appeared to be related to cardiac arrest and/or death.

5. The rate of potassium infusion may be critical in the production of potassium intoxication in these patients. Critical values could not be definitely established from the limited data at hand.

6. Since it is known that the potassium concentration of donor blood progressively increased during cold storage, the safest procedure would be to use fresh, warm donor blood at a tolerable rate.

REFERENCES

1. Tullis, J. L.: Blood Cells and Plasma Proteins: Their State in Nature, New York, 1953, Academic Press, p. 242.
2. Harris, J. E.: Influence of the Metabolism of Human Erythrocytes on the Potassium Content, J. Biol. Chem. **141**: 579, 1941.
3. Muether, R. O., Sommer, A. J., and Koster, B.: Studies on Blood Stored in Plastic Bags, Am. J. Clin. Path. **23**: 818, 1953.
4. Philipsborn, H. F., Jr., Traisman, H. S., and Greer, D., Jr.: Rupture of the Spleen—A Complication of Erythroblastosis Fetalis, New England J. Med. **252**: 159, 1955.
5. Miller, G., McCoord, A. B., Joos, H. A., and Clausen, S. W.: Studies of Serum Electrolyte Changes During Exchange Transfusion in Infants With Erythroblastosis Fetalis, Am. J. Dis. Child. **84**: 637, 1952.
6. Miller, G., McCoord, A. B., Joos, H. A., and Clausen, S. W.: Studies of Serum Electrolyte Changes During Exchange Transfusion, Pediatrics **13**: 412, 1954.
7. Overman, R. R., Etteldorf, J. N., Bass, A. C., and Horn, G. B.: Plasma and Erythrocytes. Chemistry of the Normal Infant From Birth to Two Years of Age, Pediatrics **7**: 565, 1951.
8. Graham, B. D., and Heyn, R. M.: Acid-base Homeostasis During Exchange Transfusion of Newborn Infants With Preserved Blood, Pediatrics **15**: 241, 1955.

Spare That Rod! Or, a True Son of Adam

November 6, 1692. Joseph [four years old] threw a knob of Brass and hit his Sister Betty on the forehead so as to make it bleed and swell; upon which, and for his playing at Prayer-time, and eating when returning Thanks, I whipd him pretty smartly. When I first went in (call'd by his Grandmother) he sought to shadow and hide himself from me behind the head of the Cradle: which gave me the sorrowfull remembrance of Adam's carriage.

SAMUEL SEWALL'S DIARY.

SOILING IN CHILDREN DUE TO CHRONIC FECAL IMPACTION

GERALD MASON FEIGEN, M.D.
SAN FRANCISCO, CALIF.

IT IS the purpose of this paper to demonstrate with a group of seven cases that soiling in children may be the result of chronic fecal impaction, and to suggest a method of treatment.

Soiling of the underclothes occurs in children with neurological disease which affects the anal sphincters. It has also been described as psychosomatic in origin.[1] The role of the anus in the psychologic development of the individual has been widely described, and gains derived by a neurotic child by soiling are understandable. However, the other side of this coin must be examined; children who soil because of fecal impactions have definite psychologic problems which may be deceptive.

It is a well-known fact that in adults a large impaction is often associated with the passage of a frequent, small, dark liquid stool. This is the result of the passage of liquid fecal contents downward over the impacted fecal masses; this applies in children as well. In this group of cases, the impactions were extremely sizable in length and thickness and, together with the continuous seepage, they apparently exhausted the sphincter and led to the characteristic staining of the underwear.

The bowel habits of these children were similar. Large movements occurring at intervals of from two to ten days were described. Bleeding and pain were not common. There were four males and three females, aged 3 to 9. The duration of symptoms varied from two months to four years, with an average of one year. A characteristic walk was described by four of the mothers. When the child's underpants were soiled he would walk with his knees together and move from the hips with the back slightly bent. This was in an apparent attempt to separate the soiled garment from the skin. The psychologic symptoms were similar in all cases, varying merely in degree. Isolation, withdrawal from group activity, and unwillingness to play with others were the main problems. Anxiety expressed about offensive odors, an inferiority feeling in connection with some unknown malformation, or sickness in the bowel was also common. There seemed to be no cases of psychosis or severe psychoneurosis in this group and this impression was augmented by the impressive changes in behavior following successful treatment. The parents expressed concern about the children's behavior. They too were worried about the possibility of a disease or malformation. They disliked the continual discussion of bowel movements and the odors and increased laundry occasioned by the soiling. Three children were being treated by psychiatrists for this symptom and the parents of two others were

From the Department of Proctology, Mount Zion Hospital.

UNIVERSITY OF AMERICAN LIBRARIES

considering this as a possible way out. One mother mistook the soiling for actual bowel movement and did not believe that her child was suffering from constipation.

Physical examination revealed well-nourished children. The impaction could be palpated in six cases. Digital examination was diagnostic. The sphincter was patulous, markedly in five, slightly in two. The examining finger caused no pain. The rectal ampulla and rectosigmoid were filled with a large fecal mass usually quite firm but sometimes soft and gummy. An adult-sized anoscope could be passed with no difficulty and disclosed superficial traumatic ulceration in two cases; the others were not remarkable. Proctoscopy was delayed until after the impactions were passed and there was no case that manifested any evidence of clinical megacolon. X-rays of the colon were delayed until the treatments had been well established.

A program of treatment was outlined. Traumatic areas were painted with 3 per cent silver nitrate. A well-balanced diet was prescribed, emphasizing vegetables and fruit; chocolate was forbidden and skim milk substituted for whole milk. An adequate fluid intake was stressed, including a good-sized glass of fruit juice in the morning and at least four glasses of water during the day. Fifteen to thirty drops of 1 per cent aqueous dioctyl sodium sulfosuccinate, a surface wetting agent, was prescribed twice daily in fruit juice or milk. The clinical use of this preparation (commercially known as Aerosol OT) was described by Wilson and Dickinson.[2] Extensive use of the agent in doses of less than 2 mg. per kilogram showed no evidence of toxicity. It facilitates penetration of the impacted fecal masses by water and oil, acting like a detergent. Four to 8 c.c. of flavored liquid petrolatum were prescribed twice daily for the first two weeks and was gradually discontinued. Enemas were not used.

Whenever possible the children were interviewed alone. Habit time was stressed; they were asked to get up a little earlier than usual and to go to school right after breakfast. This also prevented anxiety about being late for school. They were told that the condition was not serious, and encouraged to believe that it would soon be relieved. The parents were told to discontinue discussion about bowel movements and to show sympathy and confidence. Changes in dosages and reports on progress were made by telephone twice weekly.

RESULTS

In all cases soiling disappeared in two to three weeks. Large copious stools of great length were passed after two or three days; this continued for from seven to fourteen days at irregular intervals, and then more normal and more regular stools appeared. By the end of the first month the children averaged five stools a week. Treatment was continued over a period of three months, and dosages gradually reduced, the petrolatum eliminated first, and then the intake of dioctyl sodium sulfosuccinate reduced in dosage. Occasional relapses of constipation occurred in the first eight weeks in three cases and were treated by an increase in dosage of the medications. There were no recurrences of soiling. There was considerable improvement in sphincter tone merely upon resumption of regular bowel

habits. However, in the cases in which the sphincter was quite patulous, contractions of the sphincter were prescribed as exercises to be done twenty-five times twice daily and in all cases functional continence was established.

The psychologic improvement was dramatic. The children lost their embarrassment, returned to group play, and to what their parents considered as normal behavior. The parents were relieved and pleased; psychiatric treatment was discontinued in three cases by the parents; in the fourth case they considered other behavior problems necessitated further psychiatric care. The attitude of the psychiatrists involved varied; one forbade any physical examination, two welcomed the investigation, and one gave useful instruction in handling the particular child. It may be of help to psychiatrists treating children in whom there is a complaint of soiling, to eliminate chronic fecal impaction as a possible cause.

SUMMARY

1. A group of seven children is presented, each of whom was soiling his underclothes because of chronic fecal impaction. Their physical and psychologic symptoms are described.

2. The course of treatment involving diet, medication with dioctyl sodium sulfosuccinate, and habit time is outlined.

3. The results of treatment are uniformly good, both as to the physical and psychologic symptoms.

REFERENCES

1. Vaughan, G. F., and Cashmore, M. B.: Encopresis in Childhood, Guy's Hosp. Rep. **103:** 360, 1954.
2. Wilson, J. L., and Dickinson, D. G.: Use of Dioctyl Sodium Sulfosuccinate (Aerosol OT) for Severe Constipation, J. A. M. A. **158:** 261, 1955.

For the Ricketts

Take 9 Oz of snails boyle them together in a Littell, then take them out of their houses and putt them to a pint of milke, and boyle the milk a quator away, then give the Child of it every day as much as it will eate.

WILLIAM PENN'S "BOOK OF PHISICK."

EXPERIENCE IN SECONDARY SCREENING OF CARDIAC SUSPECTS OF SCHOOL AGE

SIDNEY FRIEDMAN, M.D., AND C. ROBERT E. WELLS, M.D.
PHILADELPHIA, PA.

IN THE state of Pennsylvania all school children are periodically subjected to a compulsory complete physical examination. From 1951 to 1955 we re-examined and reviewed the cardiac diagnoses of 4,599 children in the public and parochial schools of Philadelphia while participating in a program of secondary screening of cardiac suspects. The practical importance of accurate and current cardiac diagnoses in a school population should require no emphasis and is presently stressed by the widespread awareness of heart disease as a common cause of human suffering in all age groups, as well as by recent advances in the prevention of rheumatic fever and the surgical treatment of congenital heart disease. The initial objective of this re-evaluation was to confirm or reject the diagnosis of heart disease and, if possible, to classify the heart disease as to etiology and severity. The purpose of this report is to present briefly the cardiac findings in the 4,599 children examined and to comment on the diagnostic criteria employed as well as on the validity and usefulness of the information obtained.

From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia; and the Department of Pediatrics, School of Medicine, Temple University, and the St. Christopher's Hospital for Children.

This study was supported by a grant from the Heart Association of Southeastern Pennsylvania and achieved with the cooperation of the Division of Medical Services, School District of Philadelphia, Ruth H. Weaver, M.D., Director.

The nomenclature employed in reporting this study conforms to that recently recommended by the Criteria Committee of the New York Heart Association.[1] Accordingly, children with a history of rheumatic fever and/or chorea but without significant cardiac murmurs are classified as "rheumatic fever or chorea (inactive): no heart disease." The term "potential heart disease," formerly used to describe this clinical situation, is not used. Similarly, the term "undiagnosed manifestation" is employed to describe the situation in which symptoms or signs referable to the heart are present but the diagnosis of heart disease is uncertain. The less appropriate, previously employed designation "possible heart disease" is not used. Finally, the term "functional murmur" is discarded in favor of the more descriptive and meaningful one "innocent murmur" to indicate those cardiac murmurs which have no clinical significance.

With few exceptions, only two etiological varieties of heart disease are encountered among apparently healthy children of school age. These are rheumatic heart disease and congenital heart disease. The commonly encountered innocent cardiac murmurs of childhood[2, 3] provide another important source of diagnostic problems in this age group. Examination by physi-

cal means alone, particularly auscultation, will permit a high degree of accuracy in the diagnosis of heart disease among children of school age. This fortunate circumstance is based upon two facts; (1) that both rheumatic and congenital heart disease are almost always associated with the presence of identifiable adventitious sounds or murmurs, and (2) that it is possible by auscultatory means alone to differentiate most innocent murmurs from organic murmurs.

The incidence of cardiac disease in school populations has been determined by a variety of survey methods in a number of cities and in varied climatic areas in this country.[4-12] The findings in these studies are in general agreement with those reported in 1953 from Philadelphia by Cahan,[13] who found organic heart disease to be present in 0.62 per cent of the total enrollment of the city's public schools. Many factors may influence the outcome of a cardiac survey in a school population. Wedum and her associates[14] pointed out the important role played by the experience of the examiners and the method of selection of subjects for examination and/or re-examination. Other variables frequently mentioned are: (1) the diagnostic criteria and diagnostic facilities employed, (2) the exclusion of children too ill to attend school, (3) socioeconomic and racial factors in the group examined, and (4) irregular selection of age groups for examination.

MATERIAL AND METHODS

All of the children considered to be cardiac suspects had been previously examined on one or more occasions by either a school medical examiner or a family physician and were selected for re-examination for at least one of the following arbitrary reasons: (1) a history of actual or suspected rheumatic fever and/or chorea, (2) the presence of a cardiac murmur considered by the school or family physician to be innocent in character, (3) a diagnosis on the school health record of questionable or actual heart disease, (4) the presence of some indirect indication of heart disease. The last category was a small one containing a few children who were reported to have roentgenographic evidence of an abnormality in cardiac size or configuration and some children who had requested to be excused from physical exercise, the use of special facilities, and the like.

The 4,599 children included in this study ranged in age from 6 to 18 years. Approximately one-third of the group was Negro and the remainder white. The distribution by sex was essentially equal. By the arbitrary method of selection used, approximately one of twenty children in the school population surveyed was considered a cardiac suspect and selected for re-evaluation. At the time of the examinations (1951 to 1955) these children were enrolled in the first to twelfth grades. Each child was examined on only one occasion and by only one examiner. Approximately fifteen minutes was allotted for each examination so that ten to fifteen children could be examined in a morning session. The children were undressed to the waist and studied in both the erect and recumbent positions. Aside from a stethoscope, the only equipment used was a sphygmomanometer. The school health records were available and provided the findings of previous physical examinations as well as some information relative to the past medical history. In a

UNIVERSITY OF MICHIGAN LIBRARIES

small percentage of instances one or both parents attended the examination and provided additional historical data.

On the basis of the re-examination by the cardiac consultant, each of the suspects was placed in one of the following broad diagnostic categories: (1) no heart disease, (2) undiagnosed manifestation, (3) congenital heart disease, (4) rheumatic heart disease. The category "no heart disease" included those children with no evidence of heart disease who had a history of rheumatic fever and/or chorea, as well as those with no history of a predisposing etiological factor. The combining of these two groups was considered necessary because the diagnosis of rheumatic fever and/or chorea made in the absence of rheumatic heart disease was felt to be extremely unreliable and not subject to confirmation by any available method.

Table I. Results of Cardiac Re-evaluation of 4,599 Philadelphia School Children

Original diagnostic category	No. examined	No heart disease		Undiagnosed manifestation		Congenital heart disease		Rheumatic heart disease	
		No.	%	No.	%	No.	%	No.	%
I. Rheumatic fever Questionable rheumatic fever Chorea	1,535	1,445	94.2	9	0.6	10	0.6	71	4.6
II. Innocent murmurs	1,572	1,510	96.1	36	2.3	15	0.9	11	0.7
III. Questionable heart disease Heart disease	1,464	966	66.0	118	8.1	207	14.1	173	11.8
IV. Miscellaneous	28	27	96.5	0	0	1	3.5	0	0
Total	4,599	3,948	85.9	163	3.5	233	5.1	255	5.5

RESULTS

The results of the re-examination of 4,599 cardiac suspects of school age are summarized in Table I. In this group, 488 (10.6 per cent) were found to have organic heart disease. Rheumatic heart disease (5.5 per cent) was only slightly more common than congenital heart disease (5.1 per cent). Re-examination of these 4,599 children resulted in the transfer of 108 cases from the categories of rheumatic fever and/or chorea, innocent murmur, and miscellaneous to that of organic heart disease, and of 966 children from the category of questionable or real heart disease to that of no heart disease.

Of the 1,535 children examined because of actual or suspected rheumatic fever and/or chorea, 4.6 per cent were found to have cardiac murmurs of an organic type. The great majority (seventy-one) of these murmurs were of the variety characteristically associated with rheumatic heart disease; in ten instances the murmurs were indicative of congenital heart disease.

The group of 1,572 children who were considered initially to have innocent heart murmurs yielded only twenty-six (1.6 per cent) instances of organic heart disease. Of these, fifteen were thought to be congenital in origin and eleven, rheumatic. It was thus necessary to examine approximately sixty children with a diagnosis

of innocent murmur as made by the family physician or school medical examiner in order to detect one case of organic heart disease. Only thirty-six (2.28 per cent) children in this category were listed as having undiagnosed manifestations indicating undetermined cardiac status.

It was in the group of 1,464 children considered to have either questionable or actual heart disease that the greatest deviation existed between the primary and secondary examinations. Nine hundred sixty-six (66 per cent) of these children were considered to have no heart disease on the basis of the secondary screening examination. The vast majority of these children had innocent heart murmurs. In only 380 (25.9 per cent) of this group was the initial diagnosis of heart disease confirmed. Of these, 54.5 per cent had congenital heart disease and 45.5 per cent, rheumatic heart disease. The remaining 118 (8.1 per cent) children in this group were placed in the category of undiagnosed manifestation. As one might anticipate, it was in this category of real or questionable heart disease that the greatest number of diagnostic problems not readily solved by auscultation alone were encountered.

Among the twenty-eight children reexamined for "miscellaneous" reasons, only one case of heart disease was diagnosed.

DISCUSSION

1. *Validity of Results.*—The principal diagnostic method employed in this study was auscultation, a subjective process which provides no permanent record for later comparison or rebuttal. It is recognized that such a relatively rapid, screening-type method involving only a single examination must result in errors of both omission and interpretation. However, complete and definite diagnoses were not the primary aim in this project. Instead, emphasis was placed upon a procedure which could be applied with simplicity to a large number of subjects. It was anticipated that in a certain percentage of the cases a third and definitive examination involving the use of roentgenograms, electrocardiograms, and other facilities would be necessary.

There were, nevertheless, several observations which indicated that a relatively high degree of consistency was obtained by the method used. First, in comparing the relative distribution of diagnoses made independently by each of the examiners over the four-year period, they are found to be in very close agreement. The greatest variation in any diagnostic category is less than 2 per cent. Further, a tabulation of the results by individual years demonstrated a similar consistency. Finally, a comparison of these findings with those of Cahan[11] and Rauh,[8] who reported on the examination of a group of similarly selected children, shows very close agreement. All of these factors lend support to the assumption that auscultation can be a very valuable and accurate tool in the diagnosis of heart disease in childhood.

2. *Auscultatory Criteria Used.*—In the differentiation of innocent from organic murmurs in childhood, the criteria most likely to yield decisive information are the acoustic qualities of the murmur and the location of its point of maximal intensity over the precordium.[15] Rheumatic heart disease in this age group most commonly is responsible for the high-pitched,

blowing apical systolic murmur of mitral insufficiency. The remaining murmurs associated with rheumatic heart disease in childhood occupy some portion of diastole and offer no serious problem in differentiation from innocent murmurs which are uniformly systolic in time. The common auscultatory problem is, thus, the separation of the high-pitched apical systolic blowing murmur of mitral insufficiency from the low-pitched, musical systolic, innocent murmur of childhood. The latter was described by Still[16] as having a "twanging-string" quality and is of greatest intensity over the midprecordium, that is, to the right of the apex and to the left of the sternum in the third, fourth, or fifth interspace.

Murmurs associated with congenital malformations of the heart are difficult to differentiate with certainty from the innocent murmurs of childhood. The systolic murmurs of congenital heart disease are frequently best heard to the left of the sternum, the area in which many innocent murmurs are most readily audible. Also, the low pitch and the nondescript qualities of many murmurs of congenital heart disease are not unlike those of innocent murmurs. It is necessary, therefore, to employ different criteria in the differentiation of these two varieties of murmurs. Some useful indications of the organic nature of parasternal systolic murmurs are as follows: (1) the presence of an associated thrill, (2) audibility of the murmur over the posterior chest wall, (3) the presence of other signs of heart disease, such as cardiomegaly, cyanosis, clubbing, and the like. Admittedly, even these criteria are not infallible and in a certain number of instances it is impossible to be certain of the significance of some murmurs, especially after only a single physical examination. The majority of children placed in the category of undiagnosed manifestation presented this problem.

The differentiation of systolic murmurs of rheumatic origin from those of congenital heart disease can usually be made on the basis of the point of maximal intensity of the murmur. Most murmurs of congenital heart disease are either basal or parasternal in location, whereas the characteristic high-pitched, late systolic blowing murmur of the rheumatic mitral insufficiency is apical. The only common murmur of congenital heart disease containing a diastolic component is the machinery-type murmur of a persistently patent ductus arteriosus. This one is also sufficiently characteristic to be readily identifiable. An appreciation of the frequent occurrence of the many other innocent adventitious cardiac sounds in childhood, such as the physiologic third heart sound, reduplication of the first or second heart sound, the venous hum, and the mid-systolic click, is also essential in the evaluation of auscultatory findings in this age group.

Although the generally consistent interpretations of auscultation in this study and others tend to support the validity of the previously mentioned criteria, there is little doubt that auscultation alone is not adequate in some instances. Especially among older school children it is possible to encounter varieties of heart disease, other than rheumatic and congenital, which may be manifest by no significant cardiac murmurs. Also, at any age certain rare congenital cardiac anomalies may exist in the complete absence of murmurs of the organic

type. Examples of such rare lesions are partial anomalous venous return, Ebstein's disease, aortic septal defect, and others. It is highly unlikely, however, that significant residual cardiac damage resulting from rheumatic heart disease would be present in the absence of organic murmurs.

3. *Practical Applications of Secondary Screening.*—The clinical information gathered in this study has several important and useful applications. First, the confirmation of organic heart disease is only 25.9 per cent of 1,464 children initially suspected of cardiac disease should serve to relieve both the patient and his parents of considerable anxiety. This is perhaps the greatest single benefit to be derived from secondary screening of this type. In addition, the consequent reduction in the size of the school's cardiac register should lead to concentration of efforts and facilities on children with actual cardiac disease and should result in improved supervision.

A comparison of the diagnoses of the primary examinations with those of the secondary screening also permits several useful conclusions to be made. There was an evident tendency to overdiagnose cardiac disease in the routine school physical examinations. This resulted principally from the misinterpretation of innocent heart murmurs as those of organic heart disease. By contrast, when innocent heart murmurs were diagnosed by school examiners or by the family physicians, the index of accuracy was very high. In only twenty-six (1.6 per cent) of 1,572 such children was the cardiac diagnosis incorrect. Since the findings among patients with a history of rheumatic fever and/or chorea are subject to change with alterations in the course of their disease, such individuals should be periodically re-examined.

The relative simplicity and the low cost of a program of secondary screening of cardiac suspects deserve emphasis. It is possible for a cardiac consultant to examine a large number of children in a relatively brief interval of time. Complicated equipment and facilities are not required. The economy of such a method, especially if carried out within the structure of the school system in a large urban community, far exceeds similar programs involving special diagnostic clinics.[17] The small loss in diagnostic accuracy is more than compensated by the factor of economy and breadth of coverage. There is also a considerable saving in the psychologic trauma imposed on those children who are found to have no organic heart disease.

SUMMARY

1. Four thousand, five hundred ninety-nine public and parochial school children in the city of Philadelphia who were arbitrarily selected as cardiac suspects have been subjected to cardiac re-evaluation by a rapid method of secondary screening.

2. The results of these re-evaluations are presented and compared with the cardiac diagnoses from the primary examination. Of the total number of children examined, roughly 85 per cent were found to have no evidence of heart disease, 10 per cent had characteristic physical findings of either congenital or rheumatic heart disease, and in 5 per cent it was impossible to make a definite diagnosis by the method of examination employed.

3. Among the 1,464 children initially selected for re-examination because of real or questionable heart

disease, the diagnosis of organic heart disease was confirmed in only 25.9 per cent, demonstrating that cardiac disease had been overdiagnosed in the course of the initial routine physical examinations.

4. The methods and criteria used in this program of secondary screening of cardiac suspects, as well as the limitations and advantages of such a program, are briefly discussed.

REFERENCES

1. The Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, ed. 5, New York, 1953, Peter F. Mallon, Inc., p. 83.
2. Messeloff, C. R.: Functional Systolic Murmurs in Children, Am. J. M. Sc. **217**: 71, 1949.
3. Epstein, N.: The Heart in Normal Infants and Children, J. PEDIAT. **32**: 39, 1948.
4. Jackson, R. L.: Heart Disease in Children in a Rural Iowa County—Particularly in Relation to Rheumatic Fever, J. PEDIAT. **29**: 647, 1946.
5. Sampson, J. J., Hahman, P. T., and Halverson, W. L.: Incidence of Heart Disease and Rheumatic Fever in School Children in Three Climatically Different California Communities, Am. Heart J. **29**: 178, 1945.
6. Weiss, M. M.: The Incidence of Rheumatic and Congenital Heart Disease Among School Children of Louisville, Kentucky, Am. Heart J. **22**: 112, 1941.
7. Benjamin, J. E.: The Heart Disease Situation in Cincinnati, Am. Heart J. **2**: 637, 1926-1927.
8. Rauh, L. W.: The Incidence of Organic Heart Disease in School Children, Am. Heart J. **18**: 705, 1939.
9. Sampson, J. J., Christie, A., and Geiger, J. C.: Incidence and Type of Heart Disease in San Francisco School Children, Am. Heart J. **15**: 661, 1938.
10. Cahan, J. M.: The Incidence of Heart Disease in School Children, J. A. M. A. **92**: 1576, 1929.
11. Cahan, J. M.: Rheumatic Heart Disease in Philadelphia School Children, Ann. Int. Med. **10**: 1752, 1937.
12. Robey, W. H.: A Cardiac Survey of Children in Boston Public Schools, Nation's Health **9**: 21, 1927.
13. Cahan, J. M.: School Cardiac Census—1953, J. School Health, Nov., 1953.
14. Wedum, B. G., Wedum, A. G., and Beaghler, A. L.: Prevalence of Rheumatic Heart Disease in Denver School Children, Am. J. Pub. Health **35**: 1271, 1945.
15. Friedman, S., Robie, W. R., and Harris, T. N.: Occurrence of Innocent Adventitious Cardiac Sounds in Childhood, Pediatrics **4**: 782, 1949.
16. Still, G. H.: Common Disorders and Diseases of Childhood, ed. 3, London, 1918, Oxford University Press, p. 495.
17. Hubbard, J. P.: Pennsylvania's State Rheumatic Fever Program, Pennsylvania M. J. **53**: 620, 1950.

'Tis easy to cure excema in New England, Dr. Hill

Besides I have one of my children that was formerly most lamentably handled with sore breaking out of both his hands and feet of the king's-evill, but since he came hither hee is very well ever he was, and there is hope of perfect recoverie shortly even by the very wholesomnesse of the aire, altering, digesting and drying up the cold and crude humours of the body: And therefore I thinke it is a wise course for al cold complections to come to take physick in New-England: for a sup of New-England's aire is better then a whole draught of Old England's ale.

—NEW ENGLAND'S PLANTATION. . . WRITTEN IN THE YEAR 1629, BY MR. HIGGESON.

PREVALENCE OF HEART DISEASE AMONG SCHOOL CHILDREN IN ISRAEL

MOSHE A. SZABO, M.D., AND LUCILLE J. ROSS, M.D.*
JERUSALEM, ISRAEL

PROGRESS in preventive and therapeutic medicine has helped to diminish morbidity and mortality due to acute illnesses in children. Physicians and allied workers are consequently devoting more thought and effort to the care of children with chronic conditions, including rheumatic fever and rheumatic and congenital heart disease. In planning diagnostic and therapeutic services for these children one is helped by a knowledge of the prevalence of heart disease among the child population in the area. We have been interested in these problems among the children of Israel.

Previous relative data have been scarce. Kagan[1] cited data of the school hygiene departments, which indicated that in 1942 to 1944 the incidence of organic heart disease per 100 Jewish children was 1.5 in Jerusalem, 1.0 in Tel Aviv, and 0.7 in Haifa. Dr. Aharon Brand, of Bikur Holim Hospital, Jerusalem, has very generously put at our disposal the following unpublished data. During the course of routine physical examinations of 966 children of all ages, attending elementary schools in Jerusalem and its adjacent immigrant camps in 1953, he found the incidence of organic heart disease to be 5.27 per cent (on the basis of clinical findings).

The present survey was undertaken to try to determine the over-all prevalence of heart disease among Israeli children. This was considered of interest and importance not only per se, but also because of the unusual conditions in the country. At the time of the study, the State of Israel had been in existence for seven years, and many of its inhabitants were immigrants. Thirty-seven per cent of the children examined in this study had been born abroad; they had immigrated from thirty-eight different countries. Consequently their home cultures, socioeconomic levels, and hygienic standards varied greatly. Most of the nonnative-born children immigrated between 1948 and 1951, and upon entering the country, many lived at first in primitive temporary dwellings made of canvas, wood, or tin in "transit camps"; toilet facilities and water were usually outside the home. Although many families have moved into concrete buildings, some still live in the transit camps. Most of the children we examined lived in dwellings of one to three rooms. Families, especially of immigrants from Oriental

This study was made possible by a special grant made available by the Central Medical Committee of the Sick Fund (Kupat Holim) of the Histadrut.

Dr. H. V. Muhsam of the Department of Statistics of the Hebrew University in Jerusalem very kindly advised us on the statistical problems associated with planning and conducting the survey.

*Present address: Manhattan Cardiac Project, Bureau for Handicapped Children of the Department of Health of New York City, 341 E. 25th St., New York, N. Y.

countries, often have many children. To the extent that it is permissible to generalize, one may say that the socioeconomic standards of the Oriental immigrants tend to be lower than those of the Ashkenazic immigrants, or of the native-born population.

It would have been of considerable interest to determine whether there were differences in the prevalence of rheumatic heart disease among the children of different ethnic groups, or living in various geographic areas in Israel, or differences correlated with socioeconomic factors, but, unfortunately, the number of children which would have had to be examined to furnish statistically valid results was much greater than was feasible at present. However, examining approximately 2,500 school children, attending fifth and sixth grades in the three large cities, Jerusalem, Tel Aviv, and Haifa, could be expected to provide a statistically valid indication of the over-all prevalence of heart disease among the children of these ages in these cities. We selected these grades since the majority of rheumatic children have usually had their initial rheumatic attack by this age. The study was limited to the three cities for practical reasons; the children and their schools were much more accessible there than in nonurban areas. Forty-two per cent of the population of the country lived in these cities. The greater urban areas included some "transit camps," and we encountered wide variations in ethnic, cultural, social, economic, and housing factors among the city children.

A brief description of the climate of the cities is included to indicate the variability of this factor. Jerusalem is inland, has an altitude of 750 to 900 M., an annual rainfall of 660 mm., and an annual mean temperature of 16.9° C. The mean temperature of the coldest month (January) is 8.3°. There may be wide fluctuations (up to 15°) in the temperature on any given day. Tel Aviv borders on the Mediterranean Sea, is flat, with an altitude of 10 to 40 M. Its annual mean temperature is 20.6° and the mean temperature of the coldest month is 13.9°. The annual rainfall is 590 mm. Haifa also lies on the coast, but is hilly. The city is divided into three "levels." The upper level (Hacarmel) lies at an altitude of 350 M., has an annual mean temperature of 18.5° (11.2° in January), and 800 mm. of rain annually. The middle level (Hadar) has an altitude of 100 M., an annual mean temperature of 20° C, and 700 mm. rainfall annually. The area nearest to the ocean has a 10 M. altitude, 630 mm. of rain annually, and a mean temperature of 21° C.

METHODS

The examining team consisted of the authors, pediatricians with specialized training in rheumatic fever and heart diseases in children.* We had worked together at the Children's Cardiac Consultation Clinic of Kupat Holim in Jerusalem, and knew from our experience at this clinic that our interpretations of physical findings agreed in a very high percentage of cases. We feel that in a survey of this type it is important that the investigators have such preliminary assurance that they use similar diagnostic criteria, because of the frequency of innocent murmurs among school-aged children.

*We both had worked at St. Francis Sanatorium for Cardiac Children, Roslyn, New York, and had served as consultants in Children's Cardiac Consultation clinics; one of us (L. R.) had had a New York Heart Association training fellowship.

The number of children to be examined in each city was determined by the number attending fifth and sixth grades in the respective city. Thirteen per cent of the pupils of these grades were included in the survey. The children were examined in their schools; the latter were chosen at random from the list of schools. In each school where the team worked, one fifth and one sixth grade class were examined. If there was more than one class of the fifth (or sixth) grade in the school, one was selected by drawing lots.

Each child had a separate card on which were recorded the physical findings and results of roentgenological examination when performed, as well as identifying data, social, and medical histories. The child was asked about the type of house he lived in, the number of rooms in the house, and the number of people at home and in his bedroom, in order to obtain a picture of the "micro-climate." The information was obtained from the pupil, his school health record, and the school nurse's knowledge of him. Although the histories thus elicited were helpful, we do not consider them entirely reliable.

If a child was absent, we checked his school health card for notation of cardiac pathology at the time of previous routine medical examinations; we also asked the nurse and teacher about his health. If there was any suggestion of heart disease or rheumatic fever in the past or current history, we tried to examine him subsequently at home, at the hospital, or at the clinic. The school nurses were asked to mail follow-up reports on the cause of absence of any child who was absent longer than two days.

Each pupil was examined by one physician. If the examiner was uncertain about the interpretation of the physical findings, or if he believed that there was definite clinical evidence of heart disease, his colleague also examined the child in question.

The children were examined at rest in both the supine and the erect positions. They were not routinely exercised. The examination was confined to inspection and palpation of the precordial area, auscultation of the heart, and palpation for femoral artery pulsations; more extensive examinations were made of those children where the presence of congenital heart disease or carditis was suspected. The former was diagnosed clinically in those children in whom auscultation revealed a continuous machinery-type murmur at the upper left sternal border, or a grade 3^2 or louder harsh or rough systolic murmur, of maximal intensity at some point along the left sternal border, but not localized only to this point; these murmurs were heard in both phases of respiration, and in the supine and erect positions. If femoral artery pulsations could not be palpated, the blood pressure was measured.

Carditis was suspected in children in whom we heard any of the following:

1. Abnormalities of rhythm: "Tumultuous" rhythm, metronomic rhythm, or apparent relative prolongation of systole on auscultation.

2. Abnormalities of rate: Lability of rate or tachycardia which did not seem attributable to fear (or, in one case, possible hyperthyroidism).

Children in whom carditis was suspected were examined for fever, arthritis, subcutaneous nodules, rashes, chorea, and unusual pallor. A final

UNIVERSITY OF MICHIGAN LIBRARIES

diagnosis of carditis was made only after taking into consideration recent history and findings on our subsequent examination(s) of the child or during his hospitalization.

Roentgenological examination was performed in well-defined cases: In Jerusalem and Haifa, all children with murmurs were requested to come to a central clinic to be fluoroscoped by the examining team. In Jerusalem, 88 per cent of such children reported, in Haifa, 59 per cent. In Tel Aviv, we invited for fluoroscopy only those children in whom a clinical diagnosis of organic heart disease was made, and those about the interpretation of whose clinical findings we were uncertain. The children were fluoroscoped in posterior-anterior, left anterior oblique, and right anterior oblique erect positions. Where indicated, barium was given. Because we were aware of the error inherent in measurements made on fluoroscopy, we had teleoroentgenograms in deep inspiration made of those children who showed evidence of apparent cardiac enlargement on fluoroscopy, yet who on auscultation revealed no evidence of heart disease.

On the basis of clinical examination supplemented by fluoroscopic and teleoroentgenographic examination as described above, the children were classified in one of the following three groups:

I. No heart disease:

A. No murmur, or

B. Innocent murmur. These were usually soft systolic murmurs most frequently located either at the lower left sternal border or at the base of the heart, minimally transmitted if at all, usually varying in intensity with the phase of respiration, and often varying with change in position. Fluoroscopy, where performed, was normal.

II. Organic heart disease (either A or B):

A. There was unequivocal auscultatory evidence of congenital heart disease or of a valvular lesion. Among the latter group, the etiological agent was considered to be rheumatic fever even in the two children who had no history of the disease, since the murmur had the characteristics of valvular disease usually caused by rheumatic fever. In the children with rheumatic activity, the nature of the anatomical lesion was not included in Table III, because we were not certain whether the lesions would be permanent, or might alter as activity subsided.

B. There was definite cardiac enlargement on x-ray in the presence of a clinically innocent murmur.

III. Undiagnosed manifestation: We were unable to decide at the time of examination whether the murmurs had an organic basis or not, because they did not fulfill all our clinical criteria of organic heart disease, criteria in respect to intensity, location of maximal intensity, quality, constancy with change in position and respiration, and transmission. However, certain of the attributes of these murmurs sufficiently resembled those of organic murmurs to prevent our dismissing them as innocent. All but one of these children were fluoroscoped; the findings were normal. In this group is also included one Tel Aviv child whom we did not see who had been hospitalized for observation because of polyarthralgias and a faint apical systolic murmur. According to the hospital records, it could not be definitely established whether she had rheumatic fever or not.

OBSERVATIONS

A total of 2,556 children was examined. Their age distribution follows:

3 children were less than 10 years of age.
169 children were 10 years of age.
798 children were 11 years of age.

871 children were 12 years of age.
446 children were 13 years of age.
148 children were 14 years of age.
45 children were 15 years of age.
10 children were 16 years of age or over.

The age was not recorded on the remaining sixty-six cards.

Table I shows the distribution of the children according to their city of residence and their country of birth.

TABLE I. DISTRIBUTION OF CHILDREN ACCORDING TO CITY OF RESIDENCE AND BIRTH PLACE

	JERUSALEM		TEL AVIV		HAIFA		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Born in Israel	384	57	969	66	263	62	1,616	63
Immigrants by extraction:								
Ashkenazic	24	3	156	11	115	27	295	12
Sephardic	23	3	128	9	24	6	175	7
Oriental	246	37	203	14	17	4	466	18
Not recorded			2		2		4	
Total	677		1,458		421		2,556	

TABLE II. CARDIAC FINDINGS

	JERUSALEM	TEL AVIV	HAIFA	TOTAL
No heart disease	655	1,445	420	2,520
No murmur	498	1,243	381	2,122
Innocent murmur	157 (23%)	202 (14%)	39 (9%)	398 (16%)
Organic heart disease				
Congenital	4	3	0	7 (0.27%)
Rheumatic	8	3	0	11 (0.43%)
Inactive	3	3	0	
Active	5	0	0	
Enlarged heart on roentgenogram	7			(7)
Undiagnosed manifestation	3	7	1	11 (0.43%)
Total	677	1,458	421	2,556

(The latter was not recorded in four instances.) The immigrant children are listed as being of Ashkenazic extraction if their country of birth was one of the following: Austria, Belgium, Czechoslovakia, England, France, Germany, Hungary, Italy, Panama, Poland, Roumania, Russia, Switzerland, United States, Uruguay, or Yugoslavia. They are considered to be of Sephardic extraction if born in Bulgaria, Greece, or Turkey. Those tabulated as being of Oriental extraction were born in one of the following countries: Aden, Afghanistan, Algeria, Cyprus, Egypt, Eritrea, Ethiopia, India, Iraq, Kurdistan, Lebanon, Libya, Morocco, Persia, Sudan, Syria, Tunisia, or Yemen.

The cardiac findings are recorded in Table II. More detailed information about the children with organic heart disease is presented in Table III.

DISCUSSION

Drawing conclusions regarding the prevalence of heart disease in different groups of children from reports of different observers is hazardous, because of variations in methods of sampling and in diagnostic criteria. Bearing this in mind, we will note the findings in two recent surveys. In 1952, Maresh and associates[3] reported a clinical survey of 11,236 sixth-grade Colorado school children. They found the prevalence of organic heart disease

UNIVERSITY OF MICHIGAN LIBRARIES

TABLE III. CHILDREN WITH ORGANIC HEART DISEASE

NAME	SEX	AGE (YR.)	CITY	BORN IN	NO. ROOMS	NO. OF PEOPLE IN FAMILY	NO. OF PEOPLE IN BEDROOM	TYPE HOUSE	HISTORY OF RHEUMATIC FEVER	KNOWN TO SCHOOL HEALTH SERVICE	ACTIVE CARDITIS	ANATOMICAL LESION
Rheumatics												
J. S.	F	11	TA	Russia	2½	4	2	Concrete	−	−	No	MI; slight EH
D. G.	M	11	TA	Israel	3	4	2	Concrete	−	+	No	MI, MS, AI; EH
R. A.	F	15	TA	Israel	1½	7	5	Concrete	+	+	No	MI; EH
I. G.	M	11	Jer	Israel	2½	3	1	Concrete	+	+	No	MI; EH
L. B.	F	13	Jer	Poland	2½	?	2	Concrete	+	+	No	MI; slight EH
S. C.	F	14	Jer	Morocco	3	9	3	Concrete	+	+	No	MI; EH
S. B.	F	12	Jer	Turkey	1	8	8	Concrete	+	+	Yes	
R. A.	M	11	Jer	Iraq	2	5	3	Concrete	+	+	Yes	
S. B.	M	13	Jer	Iraq	1	7	7	Tin	+	+	Yes	
S. A.	F	14	Jer	Morocco	1	3	3	Concrete	−	−	Yes	
M. A.	F	12	Jer	Persia	2	4	2	Concrete	+	+	Yes	
Congenitals												
S. O.	M	13	Jer	Iraq	?	?	?	Concrete		−		?IVSD
A. M.	F	13	Jer	Israel	2	8	3	Concrete		+		?IVSD
L. B.	F	10	Jer	Israel	3	4	2	Concrete		+		PDA (catheterized)
S. N.	F	13	Jer	Israel	1	10	10	Concrete		+		IASD (catheterized)
A. B.	M	12	TA	Israel	2	4	2	?		+		? (postoperative)
D. K.	M	12	TA	Israel	3	4	2	Concrete		+		?IVSD
C. N.	F	13	TA	Bulgaria	2	5	1	Concrete		−		?IVSD
Enlarged hearts												
D. N.	M	12	Jer	Israel	3	5	1	Concrete				
E. C.	M	15	Jer	Israel	2	12	6	Concrete				
H. M.	M	13	Jer	Israel	1	8	8	Concrete				
B. K.	F	11	Jer	Israel	3	4	2	Concrete				
A. L.	M	15	Jer	Iraq	3	10	3	Concrete				
Z. M.	F	15	Jer	Persia	1	3	3	Concrete				
M. J.	M	11	Jer	Iraq	1	8	8	Tin				

TA = Tel Aviv; Jer = Jerusalem.
MI = mitral insufficiency; EH = enlarged heart; MS = mitral stenosis; AI = aortic insufficiency.
IVSD = interventricular septal defect; IASD = interauricular septal defect; PDA = patent ductus arteriosus.

to be 0.94 per cent; 0.66 per cent of the children had rheumatic heart disease, 0.26 per cent had congenital heart disease, and one child had combined rheumatic and congenital heart disease. Saslaw and co-authors[4] examined 1,001 10- to 16- year-old Florida school children clinically; in doubtful cases, they supplemented their findings by roentgenologic, electrocardiographic, and laboratory examinations. Five children had rheumatic heart disease and six had congenital heart disease. The authors commented that the prevalence of heart disease which they observed was of a "smaller magnitude than that found in more northern localities." The percentages of the Israeli children we examined who had rheumatic heart disease (0.43 per cent) and congenital heart disease (0.27 per cent) were similar to those noted in the Colorado and Florida areas. That the prevalence of rheumatic heart disease was similar in these three groups is particularly interesting and possibly of importance from an etiological standpoint. Many of our children had been subjected, particularly in the past, to poor environmental conditions which included semiprimitive housing facilities and restricted food rations. At the time of this study, many children still lived in crowded homes, and their families, especially the large ones, had difficulty in "making ends meet." This suggests that these factors in the children's "micro-climates" may have played a less important role in the initiation of the disease than is generally believed.

It is noteworthy that active carditis was observed only in Jerusalem children. Despite the small number of cases of carditis, the surveyed sample is sufficiently large to enable us to believe that this observation was not due to chance alone. The reason for it is not known. It may be related to the fact that the Jerusalem children were examined during the latter half of March which is at the end of the cold and rainy season and the period of higher frequency of respiratory infections. Many physicians consider such infections to be predisposing to rheumatic activity. The children of Tel Aviv and Haifa were examined well after the end of winter; the winters in these cities are somewhat less severe than they are in Jerusalem.

Four of the five children with active carditis were immigrants from Oriental countries (Iraq, Morocco, and Persia) and one came from Turkey. Some unidentified factor in their origins, or in their living conditions either prior to immigration or after arrival in Israel, may have predisposed these children to rheumatic fever. If so, it would help to explain the observed higher incidence of rheumatic activity in Jerusalem, because in this city the percentage of children of Oriental extraction in the surveyed group (37 per cent) was higher than in either Tel Aviv (14 per cent) or in Haifa (4 per cent).

The etiology of the heart disease in those children with enlarged hearts on roentgenogram, and clinically innocent murmurs, is also obscure. (Hemoglobin determinations were not made.) Perhaps these children had attacks of carditis which left no valvular damage as detectable by characteristic murmurs. It is emphasized that one should not be misled by Table II into considering this condition unique to Jerusalem children, since the case-finding technique in this respect was not the same in the three cities. Although we had planned the same type of study

UNIVERSITY OF MICHIGAN LIBRARIES

for Haifa, only twenty-three children with innocent murmurs were fluoroscoped there, as compared with 138 in Jerusalem. The reasons for this were the lower incidence of innocent murmurs among the children in Haifa and the poorer response of the Haifa children in keeping their appointments for fluoroscopy. In Tel Aviv the children with innocent murmurs were not routinely fluoroscoped.

The over-all incidence of innocent murmurs was 16 per cent, a relatively low figure compared, for example, with 36 per cent found by Maresh and associates, and 65 per cent found by Saslaw and co-authors. One cannot say why an innocent murmur is heard on any given examination of a particular child and we are unable to explain either the relatively low over-all prevalence found or the fact that the incidence of innocent murmurs was greater in Jerusalem (23 per cent) than in Tel Aviv (14 per cent), and greater there than in Haifa (9 per cent). The higher incidence in Jerusalem may be partially correlated with the relatively greater number of children of Oriental origin in Jerusalem. The combined data of the three cities show that 20 per cent of the Oriental immigrant children had innocent murmurs, while for those born elsewhere the figure was 14 per cent. However, this cannot be the whole explanation, because even among the Oriental immigrants the incidence of innocent murmurs was lower in Haifa than in Tel Aviv, and lower there than in Jerusalem. This same pattern of difference in incidence of innocent murmurs from city to city was also observed among the native-born children, and among the combined immigrant group.

Further investigation is indicated to try to solve the problems concerned with the finding of active carditis only in Jerusalem, with the etiology of the cardiac enlargement found on roentgenogram and with the different incidences of innocent murmurs.

SUMMARY

A cardiac survey was made of 2,556 children attending fifth and sixth grades in Jerusalem, Tel Aviv, and Haifa schools. Seven-tenths per cent were found to have organic heart disease on physical examination.

Grateful acknowledgment is made to the School Health Services of Kupat Holim, the Hadassah Medical Organization, the Federal Government, and the Tel Aviv-Jaffa Municipal Government who enabled us to work in the schools under their respective jurisdictions, and to the very helpful cooperation of the individual school nurses.

We wish to record our appreciation to Dr. Leo M. Taran of New York for his advice and suggestions generously given in the course of this investigation.

REFERENCES

1. Kagan, Helen: The Incidence of Rheumatic Fever in Jerusalem and the Beginnings of Chemoprophylaxis, Tr. Fifth International Congress of Pediatrics, New York, 1947; and Acta paediat. **36:** 375, 1948.
2. Levine, Samuel A., and Harvey, W. Proctor: Clinical Auscultation of the Heart, Philadelphia, 1950, W. B. Saunders Co., p. 147.
3. Maresh, George J., Dodge, H. J., and Lichty, John A.: Incidence of Heart Disease Among Colorado School Children, J. A. M. A. **149:** 802, 1952.
4. Saslaw, Milton S., Ross, Bernard D., and Dobrin, Max: The Incidence of Rheumatic Heart Disease in Native School Children of Dade County, Florida, Am. Heart J. **40:** 760, 1950.

SOME BLOOD AND SALIVARY NONPROTEIN NITROGEN CONSTITUENTS IN CHILDREN, AND DENTAL CARIES

GORDON NIKIFORUK, D.D.S., M.S., S. H. JACKSON, PH.D., M. A. COX, M.D., AND R. M. GRAINGER, D.D.S., D.D.P.D., M.Sc.D.
TORONTO, ONTARIO

BLOOD and saliva contain variable amounts of urea and ammonia. Urea is the chief end product of nitrogenous metabolism and represents "amino groups ingested (or produced in the body) in excess of requirements (or capacity) for synthesis of nitrogenous substances."[1] Ammonia is a toxic substance to mammals[2] and only trace quantities (0.004 mg. per cent) are found in whole blood. Saliva obtained by a cannula from the parotid duct contains little or no ammonia.[3] However, in resting saliva, ammonia is produced from urea, amino acids, and probably other nitrogenous compounds as a result of bacterial enzyme systems.[4]

This report presents quantitative data on blood and salivary urea and ammonia nitrogen, the interrelationship between these constituents, and their effect on dental caries. It is based on a study of ninety-four randomly selected 7-year-old children and forty 12-year-old caries-free children.

REVIEW OF LITERATURE

While early workers recognized that urea was secreted in saliva of nephritic and uremic patients, the quantitative data of these investigators is unreliable due to the inexact method of analysis. Urea is known to diffuse readily through capillary walls.[5, 6] The analyses of Marshall and Davis[7] suggested that urea was found in all tissues and body fluids in approximately uniform concentrations.

The first precise quantitative studies of the urea content of the saliva were made by Hench and Aldrich[8, 9] and Schmitz.[3] These investigators were primarily concerned with the variation of the urea content of saliva of patients having renal disorders. Hench and Aldrich[8] reported that in normal persons the combined urea and ammonia nitrogen value of saliva is 6 to 13 mg. per 100 c.c. and that this value closely approximated that of the urea nitrogen of the blood. Estimations of the combined nitrogen in the saliva was suggested as a valuable index of renal functions.[10] The same authors noted that the effect of oral hygiene was to reduce the ammonia nitrogen and increase the urea nitrogen. On standing it was observed that the ammonia nitrogen of saliva increases, while the urea nitrogen decreases.

Schmitz[3] noted that ammonia is not a normal constituent of the parotid saliva obtained direct from the parotid duct by means of a cannula. He observed that as ammonia increased, the

From the Research Institute, Hospital for Sick Children, Division of Dental Research, Faculty of Dentistry, University of Toronto; and the Division of Medical Statistics, Ontario Department of Health.

Aided by Grant No. 78B from the Sugar Research Foundation.

UNIVERSITY OF MICHIGAN LIBRARIES

urea decreased proportionally. Berkefeld-filtered saliva gave the same values for urea and ammonia just after filtration and twenty-four hours later, suggesting that the greater part "of the ammonia content of saliva is derived from urea, a result of bacterial activity."

Saliva collected one and one-half hours after a light breakfast was analyzed by Updegraff and Lewis[11] for urea, ammonia, and total nonprotein nitrogen. Their results indicated that the combined urea and ammonia nitrogen levels approached (76.1 per cent) the corresponding blood value. The average figure for salivary NPN was 13.0 mg. per 100 c.c. The salivary urea plus ammonia nitrogen comprised about 86.9 per cent of the NPN. Similar findings were reported by Maupetit[12] and Schultz and Ziegler.[13]

The hypothesis that the salivary ammonia-urea levels are associated with caries susceptibility originated with the publication of a report by Grove and Grove.[14] This report indicated that the ammonia nitrogen content of the saliva from "caries-immune" persons was higher than that from a "caries-susceptible" group. The data concerning the analytical procedures did not contain sufficiently detailed information for exact duplication by other workers. A later report by White and Bunting[15] failed to confirm the above findings. Ludwick and Fosdick[16] failed to correlate recoverable ammonia from mouth washings and dental caries.

METHODS AND MATERIALS

Collection of Blood and Saliva.—All saliva and blood samples were collected between the hours of 10:15 and 11:15 A.M. The blood samples were collected in a 0.2 ml. blood pipette and immediately transferred to a test tube containing reagents (see analytical procedures) for the preparation of the blood filtrate. The first 10 ml. of stimulated saliva were transferred to a bottle in which 1 ml. of 1 per cent solution of mercuric chloride had been dried on the walls and was used for determination of the initial saliva urea and ammonia values. A second saliva sample (10 ml.) was collected and incubated at room temperature for two hours, after which the reaction was stopped by transferring aliquots of saliva to a bottle treated as above and the ammonia and urea values estimated. All measurements were done on duplicate samples.

Analytical Procedures.—Urea was determined in blood and saliva according to the colorimetric method of Archibald.[17] The blood filtrates were prepared by using acid zinc sulfate (12.5 Gm. of $ZnSO_4 \cdot 7H_2O$ in 125 ml. of 0.25N H_2SO_4 and made up to one liter) and 0.75N sodium hydroxide solution. For saliva filtrates the amount of zinc sulfate was increased to 20 Gm. and made up to a volume as stated above. The method was checked against the hypobromide and aeration methods of Peters and Van Slyke[18] and was found suitable to permit microanalysis of urea on 0.2 ml. samples of blood and 0.5 ml. samples of saliva.

Ammonia in saliva was determined according to the diffusion method of Conway.[19, 20] The method was suitable for analysis of ammonia on 0.5 ml. of saliva. This method had previously been satisfactorily applied to analysis of ammonia and urea in saliva by Wu and Wu.[21]

Urease activity was determined by a modified Conway technique for de-

termination of ammonia. The procedure was as follows: An experimental and control Conway dish was set up by pipetting 1 ml. of 1 per cent boric acid in the central chamber. One milliliter of the substrate consisting of 1.5 per cent urea in 0.15 M citrate buffer (pH 6.6) was added into the outer chamber. The control, in addition to the above, had 0.2 ml. of 1 per cent mercuric chloride pipetted into the outer ring. The dishes were sealed with petroleum jelly–covered lids and placed in an incubator at 30° C. for one-half hour. To the test dish 0.5 ml. of saliva was added in the outer chamber, resealed, gently rotated, and incubated again for exactly fifteen minutes. Then 1 ml. of saturated potassium carbonate was added to the outer chamber, the dish resealed, mixed, and let stand for two hours at room temperature. The ammonia was then determined in the central chamber by titration with standard acid. The control dish was treated in a similar manner and the value of ammonia subtracted from the experimental dish.

A unit of urease activity was defined as that amount of urease in 100 ml. of saliva that will liberate 1 mg. of ammonia nitrogen under the conditions previously described.

TABLE I. BLOOD AND SALIVARY UREA N AND AMMONIA N VALUES* IN NINETY-FOUR 7-YEAR-OLD CHILDREN

	UREA N IN BLOOD	INITIAL UREA N IN SALIVA	INITIAL AMMONIA N IN SALIVA	AFTER 2 HOURS' INCUBATION	
				UREA N IN SALIVA	AMMONIA N IN SALIVA
Mean value and standard error	12.2 ± 0.31	5.3 ± 0.18	3.8 ± 0.16	2.2 ± 0.19	7.4 ± 0.30
Observed range	6.3 – 20.2	2.1 – 10.6	0.5 – 9.9	15.7 – 1.5	9.7 – 0.0

*Expressed in mg. per cent.

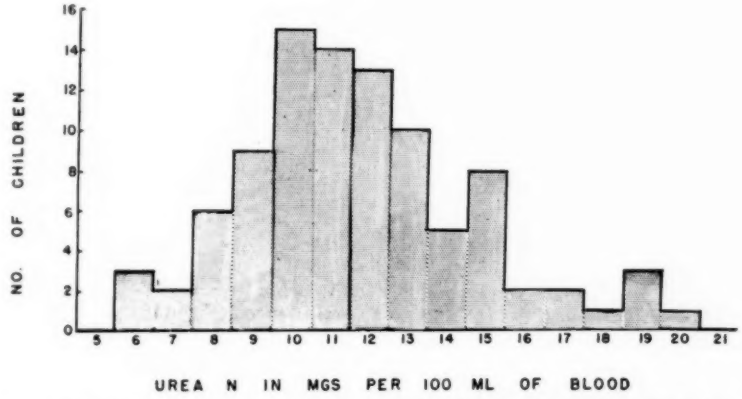


Fig. 1.—The frequency distribution curve for blood urea nitrogen in ninety-four randomly selected 7-year-old children.

EXPERIMENTAL FINDINGS

1. *Blood and Salivary Urea and Ammonia.*—Blood and salivary urea and ammonia were studied in ninety-four randomly selected 7-year-old children. In addition, the rate of urea disappearance and ammonia formation following a two-hour incubation period was measured. The mean values, standard errors, and observed ranges for these

TABLE II. LINEAR CORRELATIONS BETWEEN BLOOD AND SALIVARY UREA AND AMMONIA NITROGEN VALUES

	INITIAL UREA N IN SALIVA	INITIAL AMMONIA N IN SALIVA	UREA N + AMMONIA N IN SALIVA	AFTER 2 HOURS' INCUBATION			
				AMMONIA N IN SALIVA	UREA N IN SALIVA	PER CENT INCREASE AMMONIA N	PER CENT DECREASE UREA N
Urea N in blood	0.69*	0.11	0.59*	0.16	0.48	0.04	0.27
Initial urea N in saliva		−0.12	0.70*	−0.12	0.76*	0.07	−0.46*
Initial ammonia N in saliva			0.59*	0.78*	0.31*	0.28*	0.33*
Urea N + ammonia N in saliva				0.46*	0.40*	0.14	0.14

Number of children, 94.
*Significant at the 1 per cent confidence level.

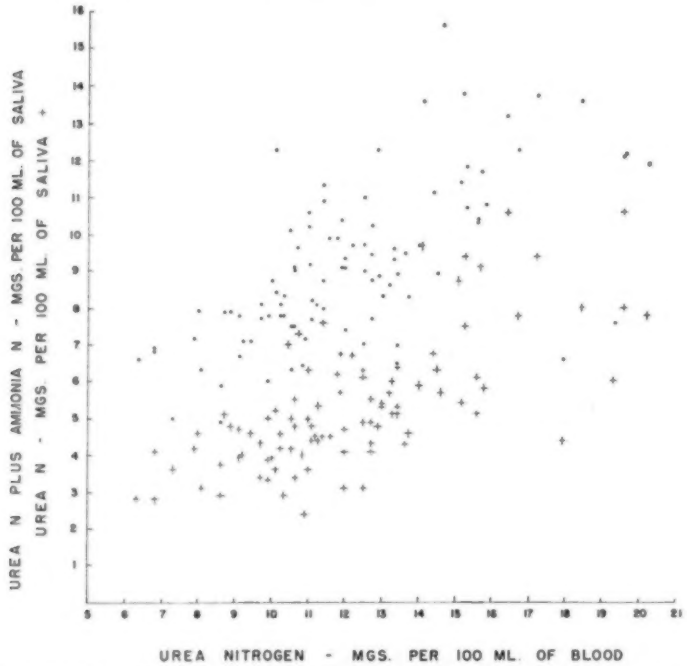


Fig. 2.—The relationship between blood urea nitrogen and (1) urea nitrogen in saliva; (2) total urea and ammonia nitrogen in saliva.

characteristics are listed in Table I. The frequency distribution curve for blood urea for this sample is shown in Fig. 1. The mean value of urea nitrogen in the saliva was 43 per cent of the blood urea nitrogen. The mean value of the sum of the urea plus ammonia nitrogen in saliva was 74 per cent of the mean blood urea.

The interrelationship between blood and saliva values is shown by the array of linear correlations in Table II. The initial salivary urea and the sum of the salivary urea plus ammonia value correlates significantly ($r = +.686$ and $+.643$, respectively) with blood urea. This relationship is graphically depicted in Fig. 2.

There was no significant correlation between initial salivary urea and ammonia values. However, the mean value of the total initial urea and ammonia nitrogen (9.1 mg. per cent) was not significantly different from the mean value of the urea and ammonia nitrogen after two hours' incubation (9.6 mg. per cent ± standard error of 0.5). Thus only 0.5 mg. per cent of the mean ammonia production of 3.6 mg. per cent or 14 per cent can be attributed to sources other than urea.

old, caries-free children from two cities. This age group was selected because their resistance to caries would appear to be more real than that of 7-year-old children. A randomly selected group of children of the same age from the same area served as a control. The quantitative data relative to blood and saliva urea and ammonia nitrogen constituents in these children is shown in Table III. The blood urea level between the control and the experimental group was significantly

TABLE III. THE RELATION OF MEAN BLOOD UREA N, SALIVARY UREA N, AND SALIVARY AMMONIA N TO CARIES-FREE AND CARIES-SUSCEPTIBLE 12-YEAR-OLD CHILDREN IN ST. CATHARINES AND MOUNT FOREST

	NUMBER	UREA N IN BLOOD* (MG. PER CENT)	UREA N IN SALIVA (MG. PER CENT)	AMMONIA N IN SALIVA (MG. PER CENT)
St. Catharines				
Caries-free	9	12.3 ± 1.19	5.2 ± 0.58	4.2 ± 0.60
Control	13	10.3 ± 0.55	4.8 ± 0.46	3.3 ± 0.25
Mount Forest				
Caries-free	17	9.0 ± 0.45	2.6 ± 0.21	4.3 ± 0.39
Control	16	7.2 ± 0.40	2.3 ± 0.25	4.9 ± 0.57
St. Catharines				
Caries-free	14	12.7 ± 0.53	5.2 ± 0.48	4.0 ± 0.60
Control	12	9.4 ± 0.67	4.1 ± 0.46	5.3 ± 0.80

*Differences are significant at 1 per cent confidence level for blood urea nitrogen between caries-free and caries-susceptible children.

2. *Relationship of Urea and Ammonia in Blood and Saliva to Dental Caries.*—

(a) *Randomly Selected Group.*—Clinical dental examinations on the ninety-four 7-year-old children were carried out in two succeeding years and included measurement of def* and DMF† surfaces and the annual caries increment. The dental caries index was not significantly correlated with blood and salivary urea and ammonia in a randomly selected group of children.

(b) *Caries-free Group.*—This study was extended to include forty 12-year-

different ($p < .01$) in each of the three groups studied. No significant difference was noted between the salivary urea and ammonia levels of the test and control groups.

3. *Urease Activity in Saliva.*—Urease in saliva was investigated because of its absolute specificity toward urea, producing ammonium carbamate which slowly hydrolyzes to ammonium carbonate.[22] The number of urease units was correlated with the initial salivary ammonia and initial urea values. Urease activity of saliva correlated significantly with total nitrogen gain after two hours' incubation ($r = +.709$) and with the nitrogen gain from urea breakdown when saliva is incubated for two hours ($r = -.433$).

*def, decayed, extracted, filled primary teeth.

†DMF, decayed, missing, filled permanent teeth.

DISCUSSION

This study was intended to clarify the interrelationship between blood urea, salivary urea, salivary ammonia, and their role in dental caries at physiological levels.

The quantitative data (Fig. 2) obtained from a study of ninety-four 7-year-old children indicates that salivary and blood urea levels are significantly correlated. This is probably explained by the fact that the urea molecule is relatively small and unionized; hence it may readily pass from the blood stream to other tissues and fluids. The amount of urea plus ammonia nitrogen in saliva is approximately 74 per cent of the blood urea nitrogen.

The data in Table I indicate that 86 per cent of the salivary ammonia was produced from urea. The remaining 14 per cent of ammonia nitrogen is most probably derived from the action of bacterial deaminases on amino acids in saliva.[4] Furthermore, a significant relationship between urease activity and ammonia production was found. The fact that there is no significant correlation between the initial urea concentration and ammonia production while the urease activity correlates significantly with ammonia production suggests that the limiting factor in ammonia production in saliva is the urease concentration.

In a randomly selected group of 7-year-old children the ammonia and urea values in blood and saliva do not correlate with the annual increment in DMF, def surfaces or cumulative DMF, def surfaces.

It was felt that a mechanism which influences dental caries should be more manifest in a caries-free than a randomly selected group of children. Accordingly, the blood and salivary characteristics, previously referred to, were also studied in forty 12-year-old caries-free children and a control group selected without regard to dental caries experience. No significant differences were noted between the test and control groups with regard to salivary urea and ammonia. However, a significant difference in the blood urea between the test and control groups was found. Since urea is the major end product of nitrogenous metabolism, it is suggested that the higher blood urea value in the caries-free group reflects a general tendency of this group to consume more protein food. Blood urea concentration, per se, was probably not related to the caries incidence, but reflected those dietary differences that appear to characterize a caries-free group. The possibility remains that real variations in the metabolic pattern, with respect to nitrogenous metabolism, explain the differences in blood urea.

There was a high urease activity in most saliva samples. The urease activity of saliva was related to the total ammonia nitrogen and the decrease of urea nitrogen when saliva samples are incubated for two hours.

This study indicates interesting interrelationships between certain blood and salivary nonprotein nitrogen constituents. The data obtained do not lend support to the hypothesis that blood and salivary urea or salivary ammonia levels were related to the cumulated caries score or the annual caries increment in the children studied.

SUMMARY

1. Quantitative data were obtained from ninety-four randomly selected 7-year-old children and forty caries-

free children with respect to the following characteristics: blood urea, salivary urea, salivary ammonia, salivary urea plus ammonia, increase in ammonia nitrogen after two hours' incubation, decrease in urea nitrogen after two hours' incubation, salivary urease activity, the cumulated caries score, and the annual caries increment.

2. A significant correlation was noted between blood urea nitrogen and salivary urea and ammonia nitrogen.

3. In the randomly selected children urea in blood, ammonia in blood and saliva, the rate of production of ammonia or the rate of breakdown of urea, and the urease activity did not correlate significantly with dental caries expressed as DMF teeth, DMF and def annual increments.

4. In a study of forty caries-free children a significantly higher value for blood urea was found as compared to a control. This was interpreted as a reflection of different dietary habits of the two groups with respect to protein and/or carbohydrate intake.

The technical assistance of Mrs. Pearl Crichton is gratefully acknowledged, and also the assistance and cooperation of the following dental and medical public health officers; Drs. C. I. Coburn, F. H. Compton, R. A. Connor, D. V. Currey, M. E. Jarret, J. W. Lawrence, and D. G. H. MacDonald.

REFERENCES

1. Cantarow, A., and Schepartz, B.: Biochemistry, Philadelphia, 1954, W. B. Saunders Co. p. 745.
2. Sumner, J. B.: Quoted in Baldwin's Dynamic Aspects of Biochemistry, New York, 1948, Cambridge University Press, p. 252.
3. Schmitz, H. W.: Comparative Concentration of Urea in the Blood and Saliva in a Series of Pathological Cases, J. Lab. & Clin. Med. **8**: 78, 1922.
4. Kesel, R. G., O'Donnel, J. F., Kirch, E. R., and Wach, E. C.: Amino Acids and their Deaminating Systems present in Human Saliva, Am. J. Orthodont. & Oral Surg. **33**: 68, 1947.
5. Van Slyke, D. D., and Dole, V. P.: Significance of Urea Clearance, J. Clin. Path. **2**: 273, 1949.
6. Galan, J. C., and Houssay, B. A.: Difusion de la urea en diferentes liquidos del organismo. Rev. Soc. argent. biol. **3**: 399, 1927.
7. Marshall, E. K., Jr., and Davis, D. M.: Urea, Its Distribution In and Elimination From the Body, J. Biol. Chem. **18**: 53, 1914.
8. Hench, P. S., and Aldrich, Martha: The Concentration of Urea in Saliva, J. A. M. A. **79**: 1409, 1922.
9. Hench, P. S., and Aldrich, Martha: Apparatus for the Determination of the Salivary Urea Index, J. A. M. A. **82**: 1194, 1924.
10. Hench, P. S., and Aldrich, Martha: A Salivary Index to Renal Function, J. A. M. A. **81**: 1997, 1923.
11. Updegraff, H., and Lewis, H. B.: A Quantitative Study of Some Organic Constituents of the Saliva, J. Biol. Chem. **61**: 633, 1924.
12. Maupetit, J.: Sur la Teneur de la Salive Humaine en Ammoniaque et en Uree, Compt. rend. Soc. biol. chem. **109**: 874, 1932.
13. Schultz, F. W., and Ziegler, M. R.: A Quantitative Study of Determination of the Combined Urea and Ammonia Nitrogen of Saliva, Am. J. Child. **31**: 520, 1926.
14. Grove, C. J., and Grove, C. T.: Chemical Study of Human Saliva Indicating That Ammonia Is an Immunizing Factor in Dental Caries, J. Am. Dent. A. **22**: 247, 1935.
15. White, J., and Bunting, R. W.: An Investigation Into the Possible Relationship of Ammonia in the Saliva to Dental Caries. J. Am. Dent. A. **22**: 468, 1935.
16. Ludwick, W. E., and Fosdick, L. S.: Ammonia Content of the Mouth, J. Dent. Res. **29**: 38, 1950.
17. Archibald, R. M.: Colorimetric Determination of Urea, J. Biol. Chem. **157**: 507, 1945.
18. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, **2**: 539, 1932, and Quantitative Clinical Chemistry, Interpretations, Urea **1**: 835, 1946, Williams & Wilkins Co., Baltimore.
19. Conway, E. J.: Absorption Apparatus for Micro-Determination of certain Volatile Substances; Determination of Urea and Ammonia in Body Fluids, Biochem. J. **27**: 430, 1933.
20. Conway, E. J., and Bryne, A.: Absorption Apparatus for Micro-Determination of certain Volatile Substances; Micro-Determination of Ammonia, Biochem. J. **27**: 419, 1933.
21. Wu, Daisy, and Wu, H.: Determination of Urea in Saliva, Proc. Soc. Exper. Biol. & Med. **76**: 130, 1951.
22. Sumner, J. B., and Somers, G. F.: Chemistry and Methods of Enzymes, ed. 2, New York, 1947, Academic Press Inc., Publishers, p. 154.

AN EVALUATION OF THE EFFECTS OF CEREBRAL PALSY ON DENTOFACIAL DEVELOPMENT, ESPECIALLY OCCLUSION OF THE TEETH

DON CHALMERS LYONS, D.D.S., M.S., PH.D.
JACKSON, MICH.

THIS study is based upon the examination of 280 children over a period of eight years at a crippled children's summer camp.* The children ranged in age from 7 to 16 years, were of both sexes, and of different races. One hundred twenty-three of the group had cerebral palsy in various degrees. The other 157 which may be considered as a control group were afflicted as follows: postpoliomyelitis 76, congenital anomalies 17, muscular dystrophy 14, Perthes' disease 11, scoliosis 5, Erb's palsy 3, miscellaneous (tubercular hip, postrheumatic fever, crippling scars due to extensive burns, congenital hemoplegia, bone infections, postbrain tumor, birth injuries, others) 31.

It is the general consensus that malocclusion of the teeth has a basic etiology in the osseus development of the facial bones, in strictly dental conditions, or is instigated by functional disharmonies or abnormalities of the facial-masticatory muscles. We are particularly interested in the latter. Dentofacial development follows this pattern; the mandible grows longitudinally from the condylar head, the maxilla's growth is dorsally with a vertical growth of the facial structures. Development of the alveolar arches is not dependent upon cranial growth for variations may be entirely independent.

The shape of the dentoalveolar arches may be influenced by function during the growth period. Nanda[8] noted that the differential rates in the gonion, gnathion, and sella-gonion arcs during childhood and adolescence are based to a considerable extent upon adaptional phenomenon. The curves of the nasion-prosthion and infradentale-gnathion are modified during childhood by the exfoliation of deciduous teeth and the eruption of the permanent. Adams[1] has observed the effect of early nutrition as an entity, prolongation of habits, time of development of muscle coordination, mouth breathing, relative tonicity of lips, size and activity of the tongue, and character of mastication on position of teeth in the arch.

Many studies have been made of the effect of muscle action on the occlusion of the teeth. The myograph has been used by a number of investigators, but Sicher[10] believes that since the myograph indicates only that the muscle is contracting, it does not indicate its role in a particular movement being investigated. A muscle may contract isotonically to produce a primary movement, or contract isometrically as a stabilizer. The myograph does not

Address: 420 W. Michigan Ave.
*Camp Tee Tonkah, Wolf Lake, Michigan.

distinguish between the two. Last[6] emphasizes the composite pattern of muscle behavior. Rix's[9] observations are of particular interest in studying the muscle action of those with cerebral palsy. He calls attention to two types of first-stage swallowing, the infantile or visceral type in which the teeth are apart with tongue in contact with resisting lips and cheek, and the adult or somatic type with teeth in occlusion and lips and cheeks passive. He noted a high percentage of malocclusion when the infantile type persisted. This type was noted in many of the children with cerebral palsy which we examined.

These factors indicate the molding influence of muscle function on occlusion during the eruption period of the teeth. It is therefore interesting to note the effects of muscle incoordination in a group of children with cerebral palsy. The variation in dentofacial-occlusal pattern in this study was in direct ratio to degree of spasticity or physical abnormality. One hundred four, or 84 per cent, of the 123 cerebral palsied children were found to have a definite malocclusion of the teeth, nineteen an average occlusion. In the latter group the disability was slight and limited almost entirely to the extremities, dental health was better, the DMF index smaller, and the child was able to give almost normal cooperation in dental treatment procedures.

Fig. 1.—Separation of maxillary incisors in case of cerebral palsy.

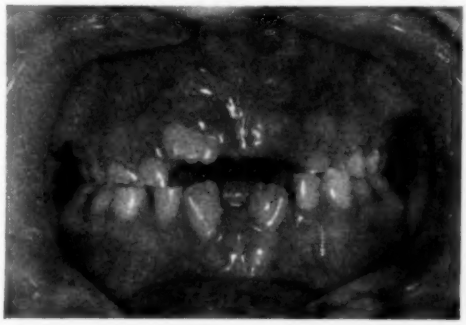


Fig. 2.—Separation of mandibular incisors, open bite, in case of cerebral palsy.

Sixty-nine children, or 66.3 per cent, of the 104 malocclusion group had a

Class II, division 1 malocclusion as demonstrated by protruding upper anterior teeth. Some of these were limited to axial tipping of the anterior teeth with little molar cuspal displacement. There seems to be definite evidence in this group of children that the infantile type of swallowing with anterior tongue thrust accounts for the occlusal change. In most cases the tongue appeared larger than normal, but it is believed that this is actually due to involuntary forward tongue positioning when the mouth is opened for examination.

Twenty-six, or 40 per cent, of this group had a separation of the maxillary anterior teeth and eleven of the twenty-six had crowded mandibular incisors, indicating the compressive forces of increased lower lip tonicity. There were fifteen, or 21 per cent, with open bite and protrusion of both maxillary and mandibular anterior teeth.

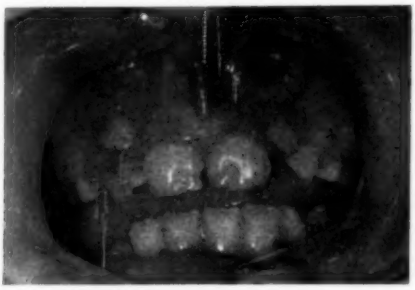


Fig. 3.—Maleruption of maxillary incisors, crowding of the teeth, narrowed arch, hypoplastic enamel of central incisors.

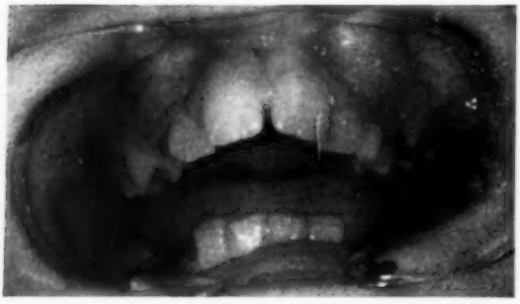


Fig. 4.

Fig. 5.

Fig. 4.—Class II malocclusion, open bite, and protruding maxillary incisor teeth in a case of cerebral palsy.

Fig. 5.—Lateral view of Class II malocclusion in a case of cerebral palsy.

In the control group of 157 children there were sixteen cases of Class II malocclusion, or only 10.2 per cent. The postpolio group contributed seven of these cases. Daniel[4] reported a group of young patients with bulbar

polio who had difficulty in swallowing, with mastication of food, and with the cough reflex, who developed Class II malocclusion. We have only one postbulbar polio in this group but a similar observation was made. Adult bulbar polio patients show no preceptible tooth movement until lack of gingival hygiene produces a chronically inflamed gingival and periodontal membrane with subsequent drifting of the teeth.

Fig. 6.—Narrowed arch with rotation of permanent maxillary lateral incisors and delayed eruption of central incisors in a case of cerebral palsy.

Fig. 7.—Narrowed maxillary arch, protrusion of maxillary teeth, open bite. Banding for orthodontic treatment in case of cerebral palsy where a degree of patient cooperation permits it.

It is of some interest, although not statistically considered, that none of the fourteen children in the muscular dystrophy group exhibited extensive malocclusion, and that each of the club-footed patients had dental anomalies: one a torus palatinus; one, delayed eruption of the permanent teeth; one, an extra wide maxillary lateral incisor; and one, eruption in line of the permanent cuspid and retention of the deciduous. All the children in the cerebral palsy group had a high DMF index (decayed, missing, filled teeth). In a previous report[7] it was noted that 20 per cent of the children's permanent teeth were decayed, missing, or filled by the age of 12.

CONCLUSION

It is believed that this group of cases demonstrates that the abnormal mus-

cle function as seen in cerebral palsy cases has a molding effect upon the positioning of the erupting teeth. Correction of occlusion in these cases is a difficult matter due to lack of ability of the child to cooperate with the orthodontist. Many cases might develop a lesser degree of malocclusion if muscle movements are controlled as much as possible by the use of available medicaments during the critical period of eruption of the permanent teeth, and if more attention was paid to preservation of teeth, particularly the deciduous ones, until their exfoliation time. General preventive dental care is possible and advised even though effective sedation and often a general anesthesia are necessary. There is a considerable amount of natural self-correction of occlusion if growth of the alveolar arches in width and length is not impeded by compressive factors, if there has been no early and often needless extractions, and if the functional anomalies of muscle action are corrected or controlled so far as possible.

REFERENCES

1. Adams, P. E.: Diagnosis and Treatment Planning, Am. J. Orthodontics **42**: 29, 1956.
2. Björk, A.: Facial Growth in Man, Studied With the Aid of Metallic Implants, Acta odont. scandinav. **13**: 9, 1955.
3. Björk, A., and Palling, M.: Adolescent Changes in Sagittal Jaw Relation, Alveolar Prognathy, and Incisal Inclination, Acta odont. scandinav. **12**: 201, 1955.
4. Daniel, R. G.: An Evaluation of the Effects of Bulbar-Spinal Poliomyelitis on Occlusion of the Teeth, Abst. Research Sect. Am. A. Orth., San Francisco, Calif., May 11, 1955.
5. Korhaus, G.: The Forces Involved in Self-Correcting Occlusal Anomalies and Their Application to Early Orthodontic Treatment, Internat. Dent. J. **5**: 3047, 1955.
6. Last, R. J.: The Muscles of the Head and Neck. A Review, Internat. Dent. J. **5**: 338, 1955.
7. Lyons, D. C.: The Dental Problem of the Spastic or Athetoid Child, Am. J. Orthodontics **37**: 129, 1951.
8. Nanda, R. S.: The Rates of Growth of Several Facial Components Measured From Serial Cephalometric Roentgenograms, Am. J. Orthodontics **41**: 658, 1955.
9. Rix, R.: Deglutition and the Teeth, Dent. Record **66**: 103, 1946.
10. Sicher, H.: Positions and Movements of the Mandible, J. Am. Dent. A. **48**: 620, 1954.
11. Watson, E. A., and Lowrey, G. H.: Growth and Development of Children, ed. 2, Chicago, 1954, The Year Book Publishers, Inc.

The Fangs of a Wolf hung about childrens necks keep them from frightning, and are very good to rub their gums with when they are breeding of Teeth. . .

The Dolphin, Bonito, or Dozado, the ashes of their teeth mixed with honey, is good to asswage the pain of breeding teeth in Children.

JOHN JOSSELYN: AN ACCOUNT OF TWO VOYAGES TO NEW ENGLAND IN 1638.

PULMONARY ENDARTERITIS WITH COR PULMONALE IN INFANCY

Report of a Case

Van Chambers, M.D., and John S. Wellington, M.D.
San Francisco, Calif.

COR pulmonale due only to endarteritis of the pulmonary arterioles is an infrequent finding. By definition, this is a disease in which, aside from the right heart enlargement, the pathologic findings are limited to the pulmonary arterioles. The most common causes of cor pulmonale in infants and children are congenital heart disease and cystic fibrosis of the pancreas; unusual causes are asthma, chest deformities, and various kinds of lung disease.

We would like to call attention to the general picture and clinical course of patients with pulmonary endarteritis, as evidenced by our case as well as those few reported in the literature as primary vascular sclerosis[1-3] or primary cor pulmonale.[4] Brill[1] in 1941 collected twenty cases—chiefly in adults. He included a few children, but no infants. Since then several other case reports have appeared[5-9]; however, we have been able to find only five reported cases of pulmonary endarteritis with cor pulmonale in infants under the age of 30 months.[2, 4, 9a] It is apparent that the syndrome is more common than reported, however,[19] and needs recognition and differentiation from other similar and more commonly found syndromes.

From the Department of Pediatrics and the Department of Pathology, University of California School of Medicine.

In general, the symptom complex and physical examination are sufficiently specific so that an ante-mortem diagnosis could be made if this condition were more often considered in the differential diagnosis of episodes of painful crying, cyanosis, and suspected congenital heart disease. The following case is presented as an illustration of this syndrome, with emphasis on those features which we feel are critically diagnostic.

CASE REPORT

K. B. was seen by us for the first time thirty minutes prior to his death and the entire history was obtained from the parents following death. This 26-month-old white male infant lived in the Central Valley area of Northern California. At the time of his birth, his mother and father were 30 and 32 years of age, respectively, and both were in good health. Family history was negative for any disease, death, or symptom complex similar to that of this child. A sibling, now 8 months of age, remains in good health.

Birth was uncomplicated; the baby appeared normal and active, was not cyanotic, and weighed 7 pounds 1 ounce. His weight gain and growth and development were considered normal until the age of 18 months, at which time his parents first noted that his fingernails, lips, and ear tips were slightly blue, and that his entire body felt cold to the touch. When the blueness became definite and persistent,

the child was taken to several doctors who each informed the parents that there was nothing demonstrably wrong; however, the blueness persisted.

At the age of 20 months his appetite became very poor and he was constantly irritable and unhappy.

At the age of 25 months he had the first "spell"—typical of others which ensued. He became cross and irritable for a few minutes, then cried as if in pain, gasped for breath, kicked his feet, and was increasingly cyanotic. Toward the end of the episode he appeared oblivious to surrounding stimuli, and finally became unconscious for a few minutes. These spells would last about five or ten minutes, after which he would be completely exhausted, sleep for about an hour, and then resume his normal activity. Because of this history and a heart murmur which was heard for the first time, an investigation for congenital heart disease was begun.

Three days before the patient's sudden death, at 26 months of age, a complete blood count had been done by the referring physician, which revealed a hemoglobin of 15.0 grams, a red blood cell count of 5,480,000, white blood cell count of 10,300 with a differential of 27 segmented cells, 66 lymphocytes, 5 monocytes, 1 eosinophil, 1 basophil, and no juvenile cells. The electrocardiogram at that time was interpreted as "an abnormal record showing supraventricular tachycardia, probably auricular tachycardia, and a pattern which is characteristic of right ventricular hypertrophy."

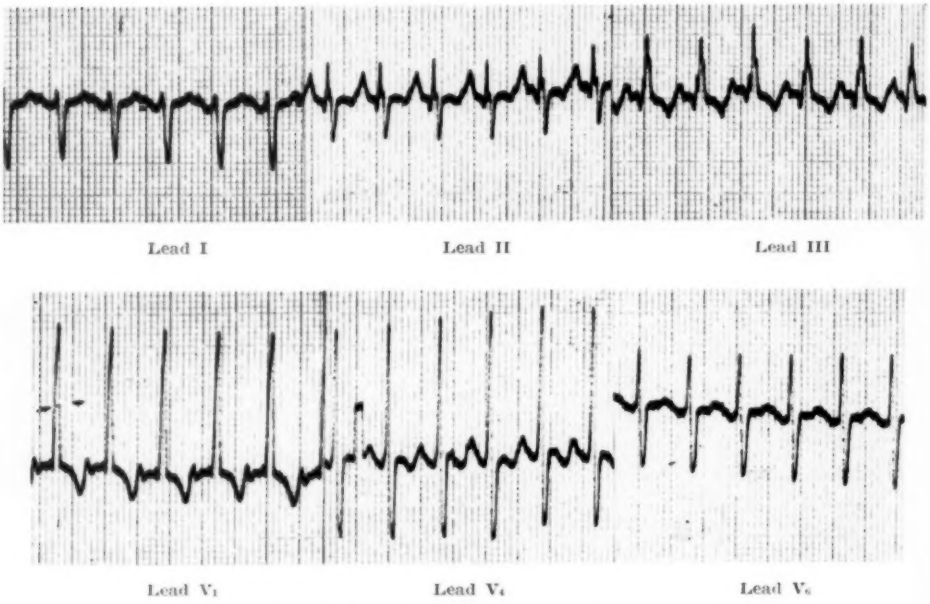


Fig. 1.—Note pattern of marked right ventricular hypertrophy.

A detailed system review revealed nothing which was referable to the central nervous system, gastrointestinal system, or the genitourinary system. However, during the last four months of life the mother had noted that the patient grunted after every respiration. He did not squat. It was her impression that some breathing difficulty was experienced—especially

with any extra physical effort—but this was not remarkable. Physicians who were consulted about this complaint did not feel it to be serious. The child had no symptoms suggestive of allergy, though he had rubbed his nose a good deal in the last two months of life. The mother had noted dry, yellow skin throughout the child's life, but consulting physicians did not consider it abnormal. There were no symptoms suggestive of hypothyroidism or vitamin lack. His medications were not unusual: he had aspirin on three occasions, he took vitamins (ABDEC) regularly, and Poly-vi-sol occasionally. At 20 months he had Trophite for a brief period and at 24 months penicillin was used on three occasions for a cold.

Physical examination was first performed by us thirty minutes prior to the patient's death. He appeared to be a well-developed, well-nourished, white male infant, who was alert but crying as if in pain. His weight was not obtained. He was not edematous. His mucous membranes were cyanotic. The chest was symmetrical. The lungs were clear to percussion and auscultation, and without râles or rhonchi. The heart was beating regularly with a normal sinus arrhythmia of 80, without a thrill, rub, or palpable impulse, though the sounds were of poor quality. The size of the heart was not determined adequately. There was a blowing Grade IV systolic murmur noted at the left sternal border in the fourth interspace. No murmurs were heard elsewhere. No splitting was noted of the pulmonic second sound. The femoral and pedal pulses were present and strong. The blood pressure in the right arm with the patient crying was 110/80. The abdomen was flat and soft; peristalsis was very slow. The liver was palpated down to the umbilicus and had a sharp edge. The spleen was not felt. The skin over the cheeks and knees was purple but elsewhere was shiny and pink. The nail beds and lips were blue. The reflexes were physiologic throughout. No laboratory tests were done, and no cultures were taken. The child died suddenly as the initial examination was being completed.

Pathological Findings.—Post-mortem examination revealed an enlarged, flabby heart which weighed 150 grams —nearly three times that of the normal. The right atrium and ventricle were markedly dilated and the thickened right ventricular wall was 9 mm. in thickness, the left 5 mm. The heart valves were all anatomically competent, but the tricuspid valve, pulmonary conus, and pulmonary artery were markedly dilated. At its bifurcation the pulmonary artery had fine, bright yellow cholesterol deposits on its intima.

The right lung weighed 130 grams, the left 110 (normal weight, 75 to 90); both were congested and a dusky red in color, but were aerated throughout. The blood vessels were prominent throughout the lung parenchyma. The remaining viscera showed marked venous congestion but no other abnormality.

Microscopic Findings.—The lungs had patchy areas of atelectasis and pulmonary edema and many alveoli contained pigmented macrophages. The pulmonary arteries showed two distinct types of change: subendothelial plaques of large foam cells resembling the lesions of systemic atherosclerosis were scattered over the intima of the major arterial branches. A different process was seen within many of the arteries which measured 300 to 400 microns, showing masses of rather loose fibrous tissue with foamy cytoplasm and concentrically disposed nuclei replacing the intima and occluding the lumina of the vessels (Figs. 2 and 3). Some of these arteries also showed thickening of the media, with separation of the internal and external laminae by a layer of thick, concentric muscle fibers. Some of the involved arteries were totally occluded, some had a small central lumen, and others were occluded but perforated with endo-

Fig. 2.

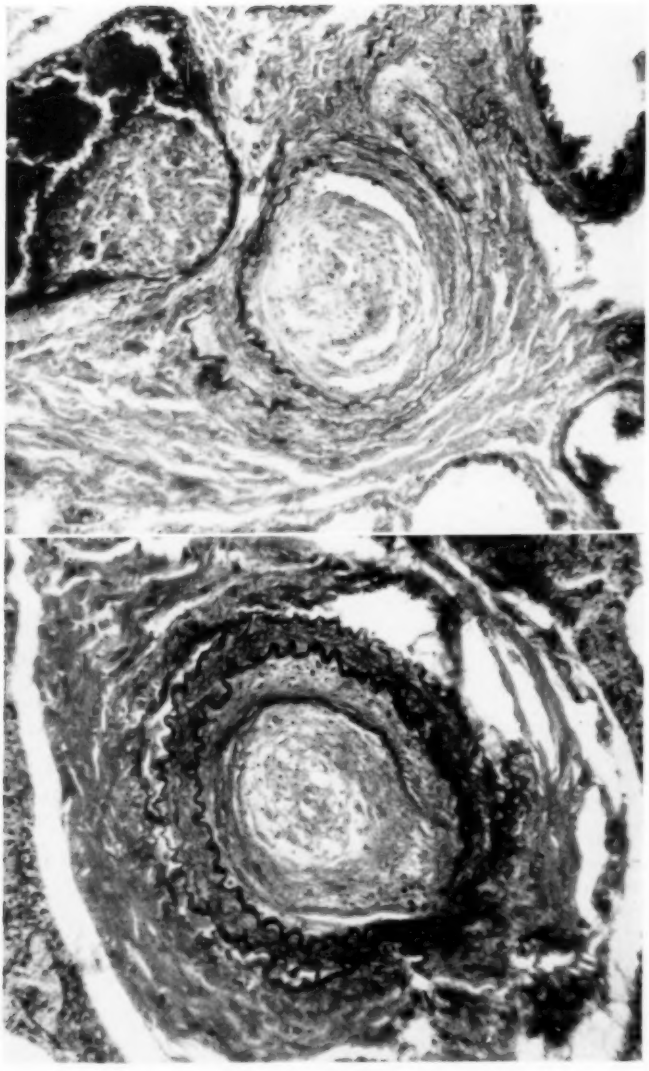


Fig. 3.

Fig. 2.—Pulmonary arteriole with cellular materials occluding lumen. (Verhoeff-Van Gieson stain; ×250; reduced ⅓.)

Fig. 3.—Pulmonary arteriole with occluded lumen and some medial thickening. (Verhoeff-Van Gieson stain; ×300; reduced ⅓.)

Fig. 4.

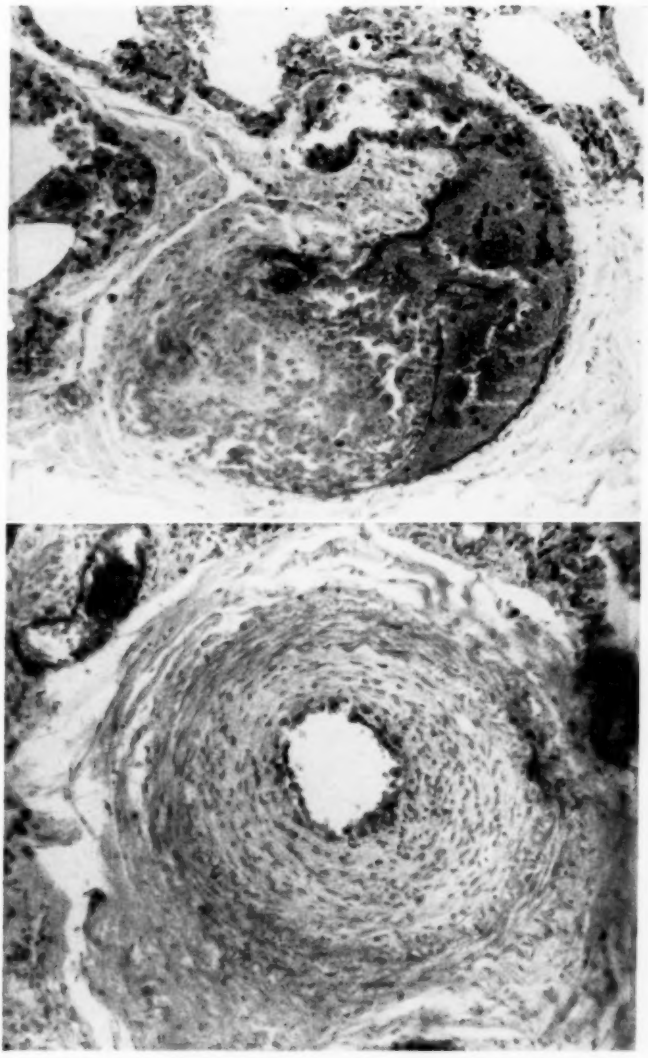


Fig. 5.

Fig. 4.—Mass of cellular material partially occluding pulmonary arteriole near a point of branching. Areas suggesting recanalization are present. (H & E; ×300; reduced ⅓.)

Fig. 5.—Incompletely occluded pulmonary arteriole without evidence of inflammation. (H & E; ×300; reduced ⅓.)

thelial-lined slits suggesting recanalization (Fig. 4). There was no inflammatory cell infiltration in or about the involved vessels (Fig. 5). There was hypertrophy of myocardial fibers of the heart and no evidence of myocarditis or fibrosis.

No significant pathologic changes were present in other organs and there was no evidence of vasculitis or vascular thickening.

DISCUSSION

In the reported cases of children under 30 months, the age of onset of symptoms varied from birth to 17 months; the age at death varied from 7 to 20 months. The usual clinical appearance at onset resembled congenital heart disease, with episodes of breathlessness and cyanosis, gradual onset of right-sided cardiac enlargement and, finally, right-sided heart failure and death. Infants manifested their disease by early nonspecific feeding difficulties, failure to gain weight, easy fatigability, and development of mild cyanosis. Our patient did not seem to have these symptoms.

When the infant is seen for these problems, a heart murmur which is loud, systolic, blowing, and located along the left sternal border in the third or fourth interspace may be noted. There may be a palpable thrill, with the pulmonary second sound loud and split, and the infant may then develop what is perhaps the most characteristic part of this picture, i.e., episodes of dyspnea, breathlessness, and increased generalized cyanosis with concomitant crying, as if in pain. This is a prominent finding and most distressing to observe. The mother will be far more upset by the apparent pain and crying than by the specific signs of breathlessness and cyanosis. In our case, we have the same impression of the cry of pain as noted by the mother, and felt it to be particularly noteworthy.

At this point, as in most of the cases previously reported, the clinical diagnosis seems to indicate either a pulmonic stenosis or an intraventricular septal defect. Investigation, however, reveals further abnormalities.[10] A chest roentgenogram may show cardiac enlargement which is confined to the right ventricle or which may, perhaps, include the right auricle. An electrocardiogram may show right axis deviation and right ventricular hypertrophy. Fluoroscopy may show enlargement of both the right auricle and right ventricle, with marked prominence of the right pulmonary artery and increased hilar markings. If cardiac catheterization is done, an increased right ventricular pressure may be noted, with a probable increase in the pressure within the right auricle.

The pathologic findings in the reported cases have consisted of (1) enormous right ventricular hypertrophy and dilatation in an otherwise anatomically normal heart; (2) evidence of right-side heart failure in visceral organs; and (3) vascular changes limited to the pulmonary arteries—usually intimal proliferation in the smallest pulmonary arterioles, sometimes in association with medial thickening or, rarely, with inflammatory infiltrate in the vessel wall ("necrotizing arteritis"). The main branches of the pulmonary arteries have sometimes shown intimal plaques similar to those noted in our case.[4, 5]

The unanswered question is whether the vessel changes are primary and, therefore, the cause of the pulmonary hypertension, or whether they are a secondary response to pulmonary

hypertension due to some entirely different cause. The evidence for the latter thesis lies largely in the similarity of the pathologic findings in the reported cases to those of patients with congenital heart disease with left-right shunt producing systemic pressures in the pulmonary circulation.[11] The principal evidence for local anatomic change in the pulmonary arterioles resulting in pulmonary hypertension in these cases is well summarized by Maxwell and Wilson.[4]

Possible causes of secondary cor pulmonale might be mentioned. In adults, any situation which causes emphysema can result ultimately in cor pulmonale, though such causes in children are rare. Recent work suggests that perhaps the most common cause in children, aside from structural anomaly of the heart, is cystic fibrosis of the pancreas, with emphysema and secondary pulmonary hypertension.[12, 14] Thoracic cage deformities and distortion of the main pulmonary arteries have also been noted, as well as patent ductus arteriosus,[15] other blood and vascular diseases such as leukemia,[12] carcinomatosis,[16] sickle-cell anemia,[12] thrombi,[17] and emboli.[18] It is interesting to note that Royce[19] rarely found asthma or tuberculosis as the cause of cor pulmonale in children nor did he note funnel chest, bronchiolitis, pertussis, or hyaline membrane disease as a cause. Cor pulmonale is rarely the result of congenital alveolar dysplasia or atelectasis of the lungs.[20, 21]

The etiology of primary pulmonary hypertension due to arteriolar narrowing is completely unknown. This process might be related to periarteritis nodosa, as evidenced by several pathologic studies suggesting a similarity in lesions.[4, 5] Two cases of periarteritis were noted to occur during acute glomerulonephritis.[7] This raises the question of sensitization phenomenon in glomerulonephritis and periarteritis and whether such an explanation could apply in some way to this disease.

The relation of this process to the collagen diseases deserves consideration, though nothing in our case is suggestive of drug or other sensitization. Infection has often been suggested, but no evidence has ever been found to prove it. Other forms of arteritis, such as Raynaud's disease and rheumatic fever, have been suggested but not confirmed. Anoxia sometimes causes vascular spasm with secondary sclerosis. A variety of emboli have been shown to cause endarteritis in animals but only a few investigators have found any evidence for such causation in the human disease. Some have suggested a retention of the narrow, thick, fetal pulmonary vessels as a causative factor.[4, 19, 22] None of these factors were found or were suggested in our case and, as in previous cases, no changes in systemic arterioles could be demonstrated. The pain exhibited by the infant (assuming he was actually in pain) might be explained as due either to coronary insufficiency because of decreased return blood flow to the left ventricle, or to myocardial anoxemia due to the lowered oxygen saturation of the blood (so-called hypercyanotic angina). In our case, there was no electrocardiographic evidence of myocardial anoxia or damage.

The etiology of this disease is not known, but hypotheses have been discussed by Maxwell and Wilson.[4] Our case does not fit into any of the previously suggested etiological categories and there is no known or suggested therapy.

SUMMARY

1. The syndrome of pulmonary endarteritis with cor pulmonale in infancy is reviewed, and an additional case is reported.

2. The disease is to be differentiated from any form of cyanotic congenital heart disease.

3. It should be noted that the infant generally does not do well, develops typical spells of increased cyanosis, dyspnea, and crying as if in pain.

4. The pathologic findings of right ventricular hypertrophy, dilatation with right-side heart failure, and sclerosis of pulmonary arterioles are discussed.

5. Etiology, pathogenesis, and treatment are not known.

REFERENCES

1. Brill, I. C., and Krygier, J. J.: Primary Pulmonary Vascular Sclerosis, Arch. Int. Med. **68:** 560, 1941.
2. Herdenstam, C. G.: Primary Pulmonary Vascular Sclerosis in Infancy, Acta paediat. **38:** 284, 1949.
3. Killingsworth, W. P., and Gibson, S.: Primary Proliferative Pulmonary Arteriolar Sclerosis, Am. J. Dis. Child. **57:** 1099, 1939.
4. Maxwell, L., and Wilson, R.: Cor Pulmonale in Infancy Simulating Congenital Heart Disease, Pediatrics **14:** 587, 1954.
5. Kirschbaum, J. D.: Pulmonary Endarteritis Obliterans With Cor Pulmonale Simulating Congenital Heart Disease. Case Report, California Med. **76:** 40, 1952.
6. Muirhead, E. E., Montgomery, P. O'B., and Gordon, C. E.: Thromboembolic Pulmonary Vascular Sclerosis. Report of a Case Following Pregnancy and of a Case Associated With Cryoglobulinemia, Arch. Int. Med. **89:** 41, 1952.
7. Kipkie, G. F., and Johnson, D. S.: Possible Pathogenic Mechanisms Responsible for Human Periarteritis Nodosa. As Suggested by the Occurrence of Two Instances of This Disease in Association With Glomerulonephritis, Arch. Path. **51:** 387, 1951.
8. Parmley, L. F., Jr., and Jones, F. S.: Primary Pulmonary Arteriosclerosis, Arch. Int. Med. **90:** 157, 1952.
9. Goodale, F., Jr., and Thomas, W. A.: Primary Pulmonary Arterial Disease. Observations With Special Reference to Medial Thickening of Small Arteries and Arterioles, Arch. Path. **58:** 568, 1954.
9a. Cross, K. R., and Kobayashi, C. K.: Primary Pulmonary Vascular Sclerosis, Am. J. Clin. Path. **17:** 155, 1947.
10. Bauersfeld, S. R., MacDonald, A. J., Berthrong, M., and Taussig, H. B.: Primary Pulmonary Hypertension, Am. J. Dis. Child. **84:** 765, 1952.
11. Valenzuela, C. T., Toriello, J., and Thomas, W. A.: Structural Changes in Intrapulmonary Arteries Exposed to Systemic Pressures From Birth, Arch. Path. **57:** 51, 1954.
12. Royce, Stephen W.: Cor Pulmonale in Infancy and Childhood, Pediatrics **8:** 255, 1951.
13. Nadas, A. S., Cogan, G., Landing, B. H., and Schwachman, H.: Studies in Pancreatic Fibrosis, Cor Pulmonale; Clinical and Pathologic Observations, Pediatrics **10:** 319, 1952.
14. May, C. D., and Lowe, C. U.: Fibrosis of the Pancreas in Infants and Children. An Illustrated Review of Certain Clinical Features With Special Emphasis on the Pulmonary and Cardiac Aspects, J. PEDIAT. **34:** 663, 1949.
15. Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F.: Syndrome of Patent Ductus Arteriosus With Pulmonary Hypertension, Circulation **8:** 15, 1953.
16. Storstein, O.: Circulatory Failure in Metastatic Carcinoma of the Lung. A Physiologic and Pathologic Study of Its Pathogenesis, Circulation **4:** 913, 1951.
17. Wartman, W. B., Jennings, R. B., and Hudson, B.: Experimental Arterial Disease. I. The Reaction of the Pulmonary Artery to Minute Emboli of Blood Clot, Circulation **4:** 747, 1951.
18. Muirhead, E. E., and Montgomery, P. O'B.: Thromboembolic Pulmonary Arteritis and Vascular Sclerosis. Its Experimental Production in Rabbits by Means of Intravenously Injected Human Amniotic Fluid and Autogenous Blood Clots, Arch. Path. **52:** 505, 1951.
19. Royce, S.: Cor Pulmonale in Infancy and Early Childhood, Am. J. Dis. Child. **82:** 228, 1951.
20. Peace, R. J.: Cor Pulmonale in Newborn Infants, Am. J. Dis. Child. **89:** 567, 1955.
21. Mallory, T. B.: Case 28401 From Case Records of the Massachusetts General Hospital, New England J. Med. **227:** 516, 1942.
22. Civin, W. H., and Edwards, J. E.: The Postnatal Structural Changes in the Intrapulmonary Arteries and Arterioles, Arch. Path. **51:** 192, 1951.

PNEUMATOSIS CYSTOIDES INTESTINALIS IN CHILDREN

Report of a Case Complicated With Fatal Pneumoperitoneum

Metine Bilger, M.D.
Istanbul, Turkey

PNEUMATOSIS cystoides intestinalis is a rare condition in children characterized by numerous air-filled cysts scattered in different regions of the small and large intestines. The size may vary from that of a small pinhead to as large as a hen's egg. The general review of literature made by Creese in 1951 revealed the existence of 210 cases in the world literature. Later, forty-two cases were added to this, amounting to 252 in all. Only forty-two of these were in children.

The case which we recently had the occasion to observe is the first one reported from Turkey. It presents all the classical characteristics and yet shows certain peculiarities which will be discussed.

CASE REPORT

E. H., a 3-month-old female infant, was admitted to the pediatric clinic, the University of Istanbul, on May 1, 1956, because of fever, mild diarrhea, and severe abdominal distention. Her birth was reported as spontaneous and normal. The family history was noncontributory, the patient being the third child, born to a mother 26 and a father 40, both of whom were in good health. One sibling had died of pneumonia at 2 months of age and another, 2 years 6 months of age, was healthy.

Her illness had started twenty days earlier as a rhinopharyngitis complicated by diarrhea which was accepted as parenteral but did not respond well to treatment. Twenty-four hours before admission, the mother had noticed an abnormal distention of the abdomen, following a severe cough. The temperature having risen shortly afterward, she was brought to the clinic for hospitalization.

The initial physical examination revealed a poor general state with a slight dyspnea and dehydration. The subcutaneous fatty tissue was diminished but the muscle tone was normal. An abnormally big and distended abdomen with obvious venous engorgement attracted immediate attention.

Her length was 55 centimeters, weight 3,550 grams, head circumference 30 centimeters, chest circumference 35 centimeters, abdominal circumference 43 centimeters, temperature 38° C., rectal, and pulse rate 126 per minute.

The lips were pale, the buccal mucosa dry, and the throat congested. The abdomen presented a balloonlike appearance with an almost transparent wall streaked with engorged veins. Extreme sonority was established with percussion. The normal dullness of the liver was absent. An abnormal bluish color was noted around the umbilicus.

The respiration was 42 per minute and very shallow. Bronchial breathing was heard at both the hili and fine crepitant râles over both pulmonary bases.

The pulse was weak but regular. Heart sounds were normal.

The nervous, urogenital, and lymphatic systems showed no abnormality.

From the Clinic of Pediatrics, University of Istanbul.

The skeletal system was normal. Large fontanel, 3 by 2 cm., open.

Admission laboratory studies showed a red blood count of 3,000,000 with a hemoglobin of 9 grams and a white blood count of 10,200. The differential count presented 60 per cent segmented leukocytes, 4 per cent young forms, 35 per cent lymphocytes, 1 per cent eosinophils and no monocytes or basophils.

Urine examination was negative for albumin, glucose, and acetone. The sediment was normal.

The tuberculin test was negative.

Fig. 1.—H. E., 3 months of age. Showing pneumoperitonitis with displacement of abdominal organs.

The stools were watery but bright yellow, with no mucus or blood. Bowel movements occurred three times daily.

In view of the findings stated above, combined penicillin and sulfonamide therapy was administered, together with Coramine and lobeline. A rectal tube and Prostigmin were used to help the enormous meteorism. Oxygen by inhalation was administered at regular intervals. No clinical change could be noted the next day and the abdominal distention had increased in spite of the almost normal stools and the free passage of gas. An x-ray examination of the abdomen was performed after a barium meal and a barium enema.

The roentgenogram revealed a diffuse pneumoperitoneum (Fig. 1). The free gas which filled all the abdominal cavity had pushed the liver and all the other abdominal organs toward the pubis. The diaphragm, although very high, showed normal movability. No fluid was noticed in the bowels and no free fluid was seen in the abdominal cavity. No abnormal findings were noted in the x-ray of the chest.

The abdominal distention and respiratory distress having greatly increased by this time, it was decided to remove some of the gas, with the help of a pneumothorax apparatus. The initial pressure within the abdominal cavity was found to be minus thirty. This fell to minus seven after the removal of 100 c.c. of gas, to minus four after 200 c.c., and to zero after 250 c.c. Exsufflation was continued and a total of 400 c.c. of gas was removed. The abdominal circumference, which was 44 cm. before the puncture, fell to 38 cm. The abdomen became soft, the respiratory distress diminished, and the general state of the patient showed a marked improvement.

Two days after the exsufflation, the abdominal circumference increased by 2 cm. and became 40 cm., although the general state of the child was quite fair. The crepitant râles were still heard at the bases of the lungs and the temperature ranged between 38.5° and 39° C.

The direct radiological examination of the abdomen performed at this time showed that free air had considerably diminished but that the bowels were extremely distended (Fig. 2).

The following day, abdominal distention having increased once again, a second exsufflation was performed. The opening pressure being zero, only 50 c.c. of gas was removed. The abdomen was quite free for the next few days, and the crepitant râles disappeared almost completely.

During the next five days, the general condition improved, the tempera-

ture showing a slight drop. The patient was able to take regular feedings and the stools were of normal color and consistency. Suddenly, during the sixth day, a marked abdominal distention developed again and the circumference of the abdomen increased to 47 cm. The patient's general state deteriorated and crepitant râles were heard again at the pulmonary bases. This induced us to perform a new exsufflation during which the opening pressure was minus ten, and 600 c.c. of gas was removed, but the distention increased again during the next half hour. The general condition deteriorated rapidly, the pulse becoming

Fig. 2.—Same patient after removal of 600 c.c. of air, showing distention of intestines.

almost impalpable, and the child died soon afterward.

The necropsy performed three hours after death gave the following findings: post-mortem rigidity was still present. The abdomen was greatly distended and the umbilicus showed a very marked protrusion. A puncture mark was seen on the left hypochondrium.

Before proceeding to the removal of the organs, a solution of methylene blue was injected by mouth under pressure with the aid of a catheter, to search for the existence of any kind of perforation in the digestive tract. The same procedure was repeated by introducing the catheter into the trachea to find if there was any connection between the lungs and the pleural or the abdominal cavities. The dye was seen to infiltrate the lung tissue and to fill the intestines without any of it passing into the peritoneal cavity, thus excluding the existence of any perforation of either the abdominal organs or the lungs.

The thymus was hypoplastic, weighing 5 grams. Edema was noted in the paravertebral basal region of both lungs while emphysematous swelling occupied the subapical mediastinal region. The heart cavities were dilated and the foramen ovale showed a pinhead-sized opening.

The intestines were highly distended with gas. Numerous gaseous cysts disseminated in the transverse colon, varying in size from that of a small pinhead to a large plum, immediately attracted attention. The transverse colon presented a real megacolon, while the descending portion showed a marked narrowing. Several scattered and superficial lenticular ulcerations were seen in the intestinal mucosa at the site of the narrowing.

The macroscopic appearance of the other organs showed no special abnormality.

The microscopic study of the ulcerations revealed swelling of the epithelial glands, desquamation of the epithelium covering the villi, shallow ulcerations of the muscularis, and infiltrative foci made up of lymphocytes, monocytes, leukocytes, and reticular cells.

Pathological diagnosis: Pneumatosis cystoides intestinalis with megacolon of the transverse colon and narrowing of the descending colon due to nonspecific ulcerations.

DISCUSSION

Pneumatosis cystoides intestinalis was first observed in adults as early as 1738 but it was not until 1904 that Maas published the first case in a child.

This disease acquired a new interest after Barjin and Dupasquier studied its radiological appearance in 1913.

The gaseous cysts of pneumatosis intestinalis are most often located in the walls of the small and large intestines and particularly in the last part of the ileum, the ascending colon, and the jejunum. In children, they are mostly seen under the mucosa and their herniated appearance into the intestinal lumen, which they sometimes obstruct, is very characteristic. In adults, however, they are located under the serosa and can be seen upon opening the abdomen.

The air filling these cysts has a composition which can be compared to the atmospheric air, giving a composition of 70 to 90 per cent N, 3 to 20 per cent O_2 and 0 to 15 per cent CO_2. The slight differences between the various records are said to be due to the reabsorption of certain elements in the various stages of the disease.

The histological aspect of the cysts resembles that of lymph spaces, but their walls sometimes contain some connective tissue with scarce elastic fibers.

The etiology and mechanism by which these air bubbles come to be formed have not yet been fully understood. Nevertheless, several theories have been put forth to explain this condition. Today the different points of view regarding the pathology of pneumatosis cystoides intestinalis can be grouped under two headings, one being the infectious, and the other the mechanical theory.

According to the relatively old bacterial, or infectious, theory, the cysts are being produced by nonpathogenic but gas-forming bacteria which travel from the intestinal lumen into the intestinal wall. This point of view is gradually being given up, as it does not explain certain points which are characteristic of the disease.

The mechanical theory, on the other hand, provides a more logical explanation. According to this theory, the air which fills the cysts has its origin in the intestinal lumen and penetrates toward the serosa by way of ulcerations or erosions of the mucosa. My colleague, Dr. Yenerman, has tried to produce the same mechanism in the cadaver and has obtained results which fully support this explanation. But the existence of ulcerations is not enough to bring about the formation of air cysts. The air accumulated in the intestinal lumen must at the same time be under high pressure as a result of constrictive processes.

The findings in our case are, like the majority of the cases in literature, in perfect accordance with the mechanical conception regarding the pathology of pneumatosis intestinalis. The existence of ulcerations of the mucosa, on one hand, and megacolon, on the other, gives a satisfactory explanation of the penetration of air and its diffusion in the form of cysts. But a point which could not be explained is the fact that the cysts, which are said to be mostly submucous in children, were found under the serosa, giving the adult pattern.

The pneumoperitoneum which complicated our case can only be the direct result of the rupture of air cysts. The results obtained from the perfusion of the lungs and alimentary tract with dye exclude the existence of any perforation capable of giving rise to pneumoperitoneum. Likewise, the gaseous cysts seen at necropsy, some of which were quite large, proves without doubt

that the collection of air in the abdominal cavity is a direct result of the rupture of these cysts. The fits of coughing which immediately preceded the first abdominal distention may have been the initial factor to start this process.

One peculiarity of our case is that the pneumoperitoneum showed a tendency to recur after the exsufflations. This can be accepted as the rupture of new cysts and it may be that the barium enemas and manual palpations might have played a part.

Would it have been possible to save the patient by performing a laparotomy? The fact that the clinical findings showed no sign of any kind of perforation and that neither the megacolon nor the cysts could be diagnosed radiologically gave no indication for surgical treatment. Nevertheless, we think that this would have been possible if the patient was seen before the pneumoperitoneum was established, when radiological image characteristic of pneumatosis was still present.

These facts demonstrate once again that pneumatosis cystoides intestinalis is a condition in which the clinical diagnosis is very difficult, and which requires more clinical and experimental investigation before the pathology can be explained in a satisfactory and convincing way.

SUMMARY

A case of a 3-month-old infant, showing pneumoperitoneum as a complication of pneumatosis cystoides intestinalis, is reported.

The necropsy findings, consisting of pneumatosis, megacolon of the transverse colon, and narrowing of the descending colon as a result of ulceration of the mucosa, tend to show that the pathology of the disease can best be explained on the basis of the mechanical theory.

REFERENCES

Botsford, T. W., and Krakower, C.: J. PEDIAT. **13:** 185, 1938.
Brunner, A., et al.: Traite de chirurg., Lausanne, 1951, Delachaux, Publishers.
Chiary, M. Sonnon: Presse méd. **44:** 1771, 1936.
Creyssel, J. Maillet, P., and Meunier, M.: Lyon chir. **43:** 4, 1948.
Dale, W. A., and Pearse, N. E.: Surg., Gynec. & Obst. **90:** 215, 1900.
Finney, J. M. T.: J. A. M. A. **51:** 1291, 1908.
Friedmann, I.: J. Clin. Path. **2:** 91, 1949.
Gazin, A. I., Brooke, W. S., Lerner, H. H., and Price, P. B.: Am. J. Surg. **77:** 563, 1949.
Jones, J. D. T.: Brit. J. Surg. **36:** 141, 1948.
Judge, D. J., Cassidy, J. E., and Rice, E. C.: Arch. Path. **48:** 206, 1949.
Lenorment: Presse méd. **11:** 1208, 1920.
Lerner, H. H., and Gazin, A. I.: Am. J. Roentgenol. **56:** 464, 1946.
Lerner, H. H., and Price, P. B.: Am. J. Surg. **77:** 563, 1949.
Lewis: Practice of Surgery, Hagerstown, Md., 1945, W. F. Prior Co., vol. VII, chap. 8.
Lindsay, J., Rice, W. C., and Salingli, M. A.: Arch. Path. **30:** 1085, 1940.
MacKenzi, E. P.: Peditrics **2:** 537, 1951.
Masson, P.: Rev. med. Suisse Rom. **44:** 546, 1924.
Masson, P.: Ann. anat. path. **2:** 541, 1925.
Moore, R.: Am. J. Dis. Child. **38:** 818, 1929.
Öktem, Ibrahim: Klinik **2:** 7, 1943.
Pybus, F. C.: Brit. J. Surg. **21:** 539, 1934.
Reverdin: Rev. med. Suisse Rom. **44:** 546, 1924.
Schon, S., Ullman, T., and Laufer, S.: Arch. Int. Med. **88:** 362, 1951.
Sherwin, B., and Messe, A.: Ann. Surg. **136:** 893, 1952.
Stiennon, O. A.: Am. J. Dis. Child. **81:** 651, 1951.
Urban: Wien, med. Wchnschr. **30:** 1750, 1910.
Wainwright, J.: Arch. Dis. Childhood **26:** 164, 1951.
Yenerman, M.: Report to the Fifth Cong. of Int. Comp. Anat., Istanbul, 1949.
Ziegler, F.: Chirurg. **5:** 19, 1948.

DISCORDANT MONOZYGOTIC TWINS

Disparity in the Cardiac Status

Harold E. Stadler, M.D., and Walter Chroniak, M.D.
Indianapolis, Ind.

THE disparity in the cardiac status of identical twins has been previously described,[1-3] but the rarity of such an occurrence justifies this report.

CASE REPORT

Shirley (the affected twin) and Sharon W. were born on Oct. 2, 1949. Sharon weighed 5 pounds 10 ounces, and Shirley 5 pounds 13 ounces at birth. Shirley had a cyanotic episode requiring oxygen shortly after she went home but following a several-day period in the hospital was not affected again. Her murmur was noted by the family physician about two years ago. The parents were not impressed by a difference in the development of the two girls and even their schoolwork was accomplished in a strikingly similar manner and upon an almost identical level.

Sharon was 44 inches tall and weighed 34 pounds. Her occipitofrontal circumference was 19¼ inches. There was an inconstant internal squint on the left side. The blood pressure was 90/60 mm. Hg. Shirley was 44 inches tall and weighed 32 pounds. Her occipitofrontal circumference was 19¼ inches. There was an inconstant internal squint on the left side. The heart borders could be

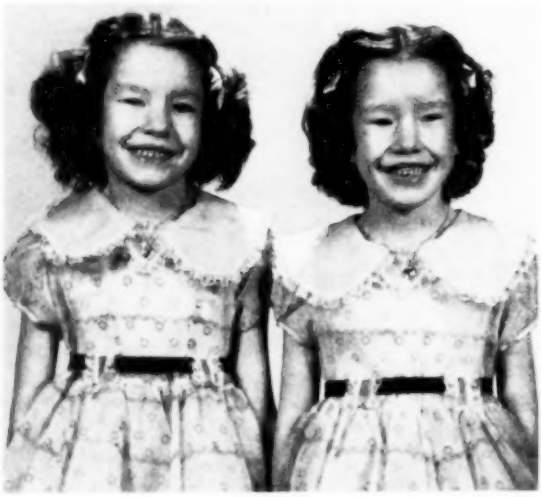


Fig. 1.—Photograph of the twins, with Shirley (the affected member) on the reader's right.

This study was made possible by a grant from the United States Public Health Service: Heredity and Congenital Heart Disease-623D.

Address: 6244 Washington Blvd.

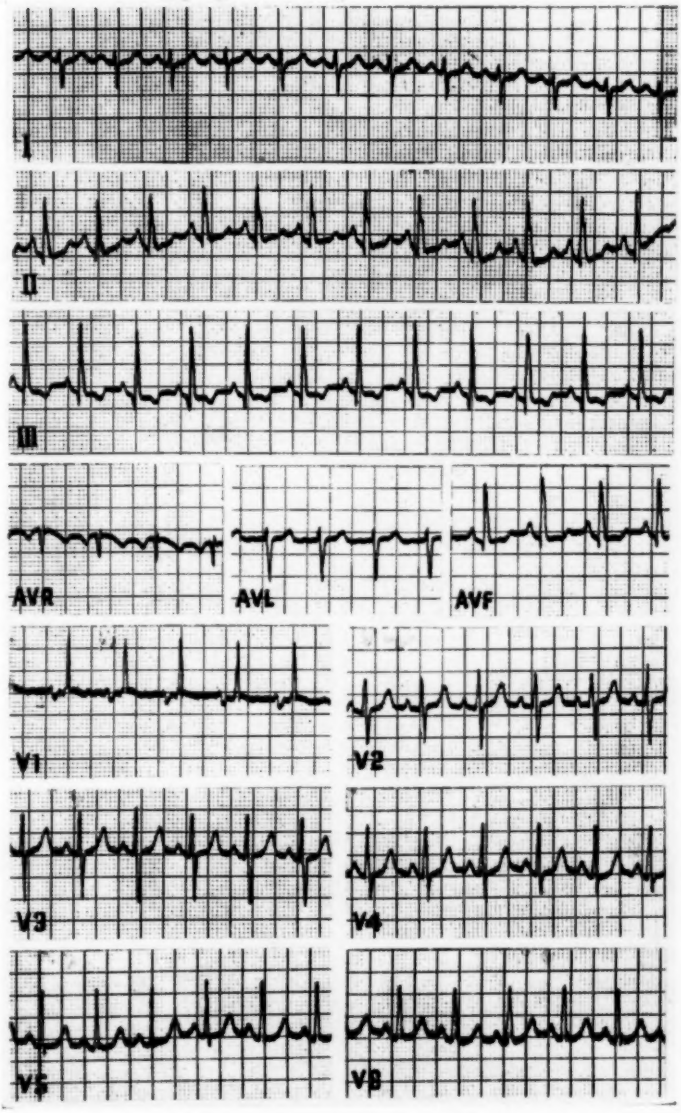


Fig. 2.—Shirley's electrocardiogram taken on Feb. 13, 1956.

percussed slightly outside of the normal limits. A thrill was palpable over the upper sternum. There was a loud murmur, which was harsh in quality. The blood pressure was equal in the arms, 95/65 mm. Hg.

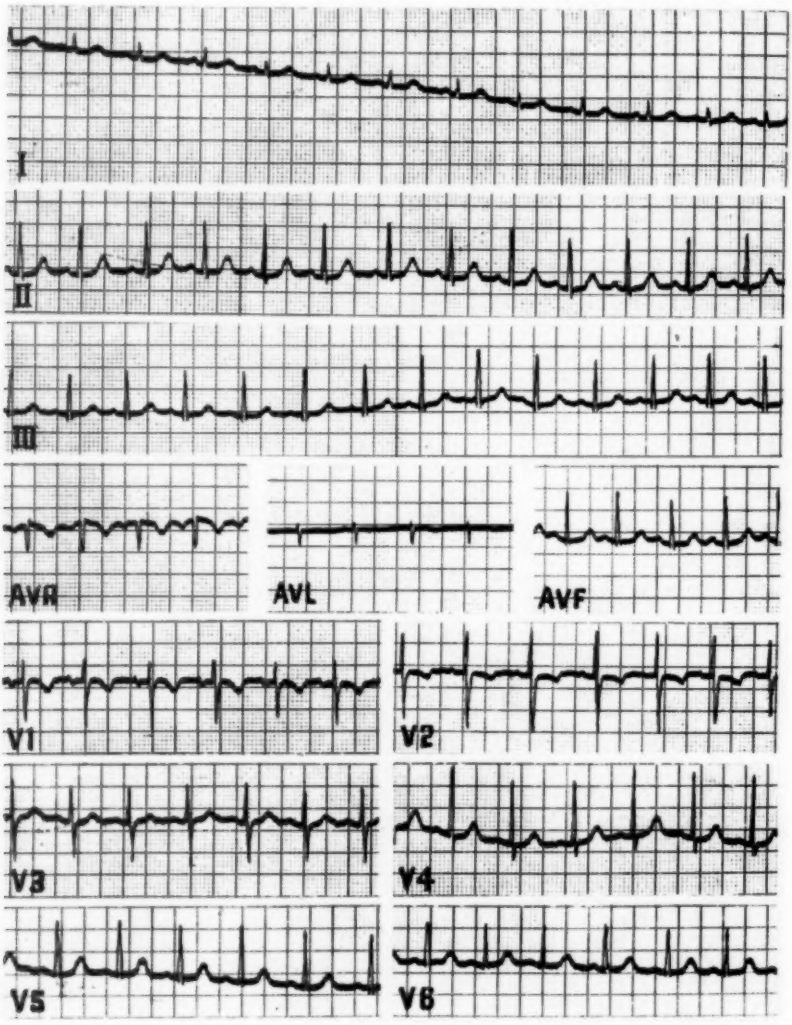


Fig. 3.—Sharon's electrocardiogram taken on Feb. 13, 1956.

generalized systolic murmur which could be heard over the entire precordium but which had its maximum intensity over the second left interspace. All cardiac sounds with the exception of M_1 were obscured by the

The posterior tibial and dorsalis pedis pulsations were strong. Exercise did not cause cyanosis of the skin or mucous membranes, or shortness of breath. Clubbing of the fingers or of the toes was not present.

Roentgenograms of the girls' chests were made and while Sharon's x-ray (Fig. 5) was normal, Shirley's was noted to show a globular cardiac configuration with enlargement. Fluoroscopy added useful information, in that the right ventricle was found to be enlarged and the auricles were found to be within normal limits. The esophagram was normal. The pulmonary arteries were thought to be reduced in caliber. An abnormal position of the aorta was not demonstrable.

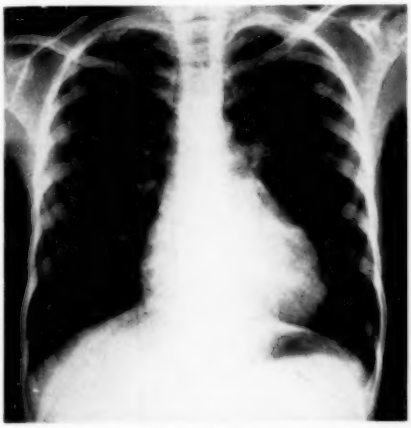


Fig. 4.—Shirley's chest x-ray showing abnormal cardiac configuration.

Fig. 5.—Sharon's chest x-ray.

Sharon's electrocardiogram (Fig. 3) showed no disturbance; however, Shirley's tracing showed evidence of the following deviations:

1. Right axis deviation.
2. Right ventricular hypertrophy.
3. High and pointed P waves in limb leads II and III, indicating some right auricular hypertrophy (not consistent with fluoroscopic findings).
4. Vertical heart (rS pattern in aVL).
5. Extreme clockwise rotation of the heart (large R waves in V_1 and tall R waves in aV_F with slightly depressed RS-T segments).

The combination of these findings is compatible with the diagnosis of congenital heart disease, particularly with atrial septal defects and the tetralogy of Fallot. The clinical findings of ventricular hypertrophy, attenuation of the pulmonary arteries, the localization of the murmur, and the absence of the pulmonic second heart sound also suggest the diagnosis of tetralogy of Fallot.

The blood typing of the two girls was reported as follows:

	D	C	E	c		
Sharon W.	0	+	0	+	+	Rh+ (R_2r)
Shirley W.	0	+	0	+	+	Rh+ (R_2r)

SUMMARY

Another instance of discordant monozygotic twins is here presented. The cardiac lesion had not up to the time of report exerted a detrimental effect upon the development of the affected member of the pair.

We are indebted to Dr. Philip Levine, Ortho Research Foundation, Raritan, N. J., for the blood typing. Dr. Maurice Manalan gave us the radiographic interpretations.

REFERENCES

1. Stadler, Harold E.: J. PEDIAT. **47**: 353, 1955.
2. Wade, G.: Brit. Heart J. **14**: 475, 1952.
3. Debreuil-Chambardel: Presse méd. **35**: 1157, 1927.

HEPATITIS IN THREE SIBLINGS

Possibility of Intrauterine Transmission

Alice Gamble Beard, M.D.
Little Rock, Ark.

IN RECENT years interest has arisen in the possibility of intrauterine transmission of the virus of serum hepatitis as a cause of neonatal jaundice and a possible cause of familial cirrhosis. The following report of a physician's family is presented because of the history of hepatitis in the mother and subsequent hepatitis in all three of her offspring. The third child, whose history forms the body of this report, died in hepatic failure at 2½ months of age.

CASE REPORT

A 76-day-old white male was admitted to a Texas hospital on Sept. 6, 1954, with the history of deepening jaundice and irritability of four days' duration. Blood-streaked vomitus, dark scanty urine, and acholic stools were noted the day before admission.

The patient was born of a spontaneous delivery at term, weighing 3,260 grams. The immediate neonatal period was complicated by moderate cord hemorrhage, but no transfusion was given, and the hemoglobin at no time fell below 10 grams. Because of the mild eczema, the baby was fed a formula of Mullsoy but for the month before admission had been taking an evaporated milk formula, vitamins, and cereals.

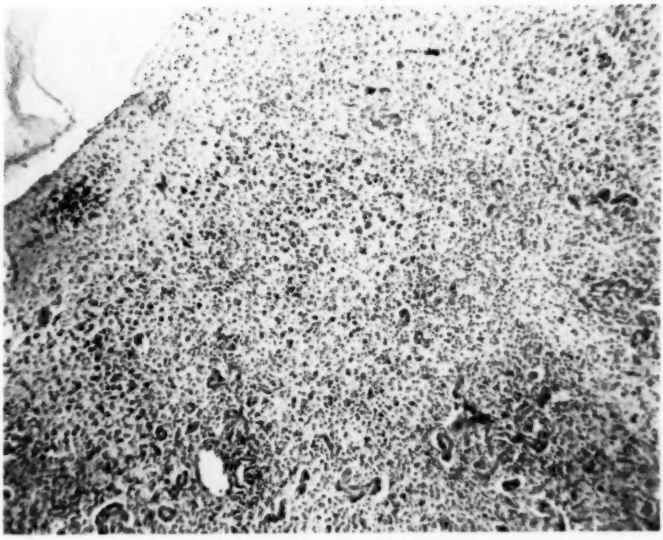
Physical Examination.—The child was a well-developed 76-day-old male (weight 5,520 grams) who appeared lethargic, dehydrated, and deeply icteric. The temperature was 37.8° C., pulse 110, and respirations 45. He was hypertonic when disturbed. Respirations were labored but no râles were heard in the chest. There were petechiae on the soft palate and blood oozed from a heel prick done six hours earlier. The liver was tender and extended 4 cm. below the right costal margin. The tip of the spleen was felt.

Laboratory Findings.—On admission the hemoglobin was 13 grams, red blood cells 4.6 million, leukocytes 23.7 thousand with neutrophils 49 per cent, lymphocytes 45 per cent, monocytes 1 per cent, and band forms 5 per cent; serological tests for syphilis, negative; blood type Rh-positive, Group B; bleeding time 14 minutes, clotting time 7 minutes; total serum bilirubin 8.0 mg. per cent, of which 1.2 mg. per cent was direct-reacting; and icterus index 60 units. The following morning, after fluid therapy, the leukocytes numbered 14.7 thousand and the hemoglobin was 11 grams. Serum sodium was 138 meq. per liter, CO_2 combining power 19.1 meq. per liter, blood urea nitrogen 5.0 mg. per cent, serum calcium 7.6 mg. per cent, and blood culture—no growth.

Course in Hospital.—The condition of the patient was not improved by the parenteral administration of molar lactate, dextrose 5 per cent in distilled water, and blood. Calcium gluconate, vitamin K, penicillin, and streptomycin were all given intensively. On the second hospital day the urine output became scanty. The child developed generalized edema, and be-

From the Department of Pediatrics, University of Arkansas.

Fig. 1.



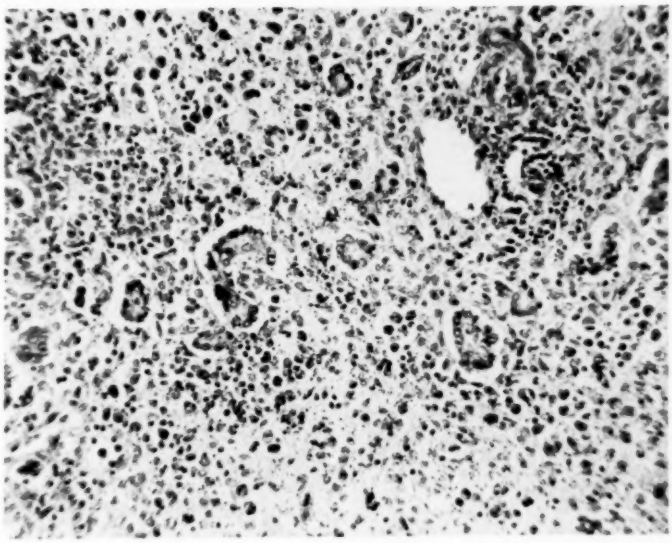


Fig. 2.

Fig. 1.—Low power. Necrosis with complete loss of lobular pattern with bile duct prominence and "reduplication."

Fig. 2.—Medium power. Note the faint outline of degenerating hepatic cells and lymphocytic infiltration around the portal spaces.

came comatose. Intramuscular cortisone 35 mg. produced no change in the coma, edema, or difficult respirations. The child's condition continued to deteriorate; he became cyanotic and died fifty-four hours after admission.

Pathological Examination.—The liver weighed 112 grams, was reddish brown, rubbery, and had a gritty texture when cut. The extrahepatic biliary tree was patent. Dye, when injected into the depth of the liver, appeared at the duodenal opening.

Microscopic sections of the liver showed almost complete destruction of the normal architectural pattern (Figs. 1, 2, and 3). Within most lobules only reticulum, bile-containing macrophages, and a few liver cells which were pale-staining and hard to visualize remained. Occasionally, intranuclear inclusion bodies were seen around the bile ducts. Lymphocytic infiltration around the portal spaces was noted, as well as marked proliferation of the bile ducts (Figs. 1 and 2). The only other findings of note were swelling of the kidney tubules and a cellular infiltrate about some of the bronchioles in the lungs.

Family History.—The 36-year-old mother had hepatitis with jaundice at 13 or 14 years of age, but had been in good health since. She could remember no antecedent injections and felt sure she had had no transfusions of blood or blood derivatives. The father was a diabetic, well controlled on insulin. Both parents were Rh-positive, the mother had Group O blood, and the father Group B blood.

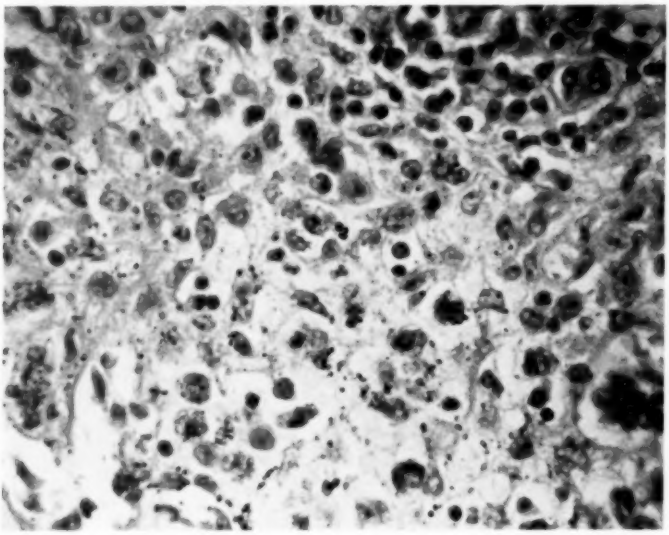


Fig. 3.—High power. Scattering of pigment-laden macrophages, amorphous cellular debris, and necrosis of hepatic cells.

The oldest sibling, a girl who was born Oct. 1, 1951, had a three-week period of jaundice, vomiting, and irritability at 2½ months of age. A large, tender liver and light stools were noted at this time, but these abnormal findings subsided gradually without treatment. The child has seemed normal since.

The second sibling, a girl who was born Oct. 15, 1952, had, at 2 months of age, a similar, though milder, period of jaundice and irritability which improved spontaneously. She

has also developed normally. Physical examinations of both children in October, 1954, revealed no abnormalities. Tests for liver function on the mother and the two girls are shown in Table I.

DISCUSSION

There is no evidence that infectious hepatitis is transmitted transplacentally, and mothers suffering with infectious hepatitis during pregnancy deliver normal babies.[1, 2] Viremia in infectious hepatitis is transient and rapidly disappears with the production of antibodies. Thus, gamma globulin is an effective carrier of infectious hepatitis antibodies, but does not prevent serum hepatitis,[3] since no antibodies can be demonstrated in the blood of patients with this disease. Viremia, capable of producing serum hepatitis, is present for long periods of time in apparently healthy people, as evidenced by multiple cases of serum hepatitis traced to a single donor,[4] reports of serum hepatitis following smallpox vaccination,[5] yellow fever immunizations,[6] tatooing,[7] diabetic clinic routines,[8] measles prophylaxis,[9] and the administration of thrombin derivatives.[10] Numerous cases of homologous serum jaundice in infancy have been reported following transfusions of pooled plasma, whole blood, or blood derivatives.[11]

The possibility of intrauterine transmission of the serum hepatitis virus has been postulated to explain the hepatitis occasionally seen in infants in whom no other adequate cause of liver involvement could be found.[12-20] This possibility was enhanced by Stokes' report of the case of an infant who became jaundiced at 2 months of age and died at 18 months of age with advanced cirrhosis of the liver. The serum of the infant and of the mother were each injected parenterally into five volunteers. Hepatitis developed in two of the five receiving the infant's serum and in three of the five receiving the mother's serum. About three years after the infant's birth, serum from the mother was again given five volunteers, of whom three developed hepatitis.

TABLE I. LIVER FUNCTION TESTS DONE ON THIS FAMILY IN OCTOBER, 1954

NAME	CEPH. FLOC.	THYMOL TURBIDITY	INDIRECT COOMBS	BILIRUBIN 1 MIN. & TOTAL	TOTAL PROTEIN	BLOOD GROUP
Mrs. S., 22 yr. after jaundice	2+	2 units	Neg.	0.0 0.2 mg. %	7.00 4.6A 2.4G	O Rh-pos.
First girl, 3 yr. after jaundice	4+	1 unit	Neg.	0.0 0.2	6.1 4.7A 1.4G	B Rh-pos.
Second girl, 2 yr. after jaundice	Trace	1 unit	Neg.	0.0 0.1 mg. %	6.0 4.7A 1.39	O Rh-pos.

In several instances, more than one sibling has had symptoms of hepatitis.[14, 16, 17, 19, 20] The first report[16] concerned a nurse who had hepatitis in 1944. Her first child, born in 1949, was jaundiced for some time after birth, but eventually recovered. Her second child became jaundiced immediately after birth and died in the

neonatal period. The parenchyma of this child's liver was almost completely destroyed. In the second family[17] the mother's first two children both lived less than two days, were not jaundiced, but had generalized edema, and cyanosis. Microscopically, the livers of both infants showed marked autolysis and necrosis. The mother's third pregnancy resulted in a macerated stillborn infant, whose liver on examination revealed changes consistent with advanced hepatic destruction. In the third family group[19] the first infant lived two days. Post-mortem examination revealed pulmonary atelectasis. The second pregnancy terminated in an abortion at three months. The third and fourth children lived six and forty-five hours, respectively.

The livers of these infants on microscopic examination showed multinucleated syncytial cytoplasmic masses in the hepatic parenchyma. This third family group has also been reported by Krainin and Lapan[20] who add that this mother, although never having had a history of jaundice, had a 4-plus cephalin flocculation test repeatedly and that a section of her liver obtained by needle biopsy showed what they described as 1-plus liver damage.

The fourth group[14] included three siblings who died at 2, 3, and 8 months of age with symptoms that simulated obstructive jaundice. At post-mortem examination, however, the microscopic findings showed multinucleated giant cells and inflammatory cell infiltration. Two siblings, born between the first and second affected children, seemed normal, but had 4-plus cephalin flocculation tests one year after the death of the third sibling. The mother of these children also had a 4-plus cephalin flocculation test but gave no history of previous jaundice. Gellis[26] comments upon the difficulty of explaining these "skip cases" in families with other siblings apparently affected by the intrauterine transmission of the homologous serum virus, unless the viremia is inconstant or the passage of the virus is determined by the condition of the placenta.

The mother of the family reported here had a 2-plus cephalin flocculation test, suggestive evidence of liver damage. Although she had a history of jaundice twenty-two years before her last pregnancy she may also have had an inapparent infection later with serum hepatitis. A 4-plus cephalin flocculation test was present in the first sibling three years after her attack of jaundice. The second sibling had only a trace reaction in this same test two years after her history of mild jaundice. Positive flocculation tests in the mothers of affected children have been noted by others,[14, 20] and when found in siblings also add weight to the consideration of a transplacentally induced disease.

Parenchymal giant cells in the liver are a common finding in many of these cases of suspected neonatal viral hepatitis. They have also been demonstrated in the livers of patients with erythroblastosis and hemolytic anemias.[21] The livers of patients whose hepatitis runs a fulminating course[16, 17, and our case] reveal changes microscopically more consistent with advanced necrosis and autolysis of liver cells as described by Lucke[23] and Wood and

Block.[23] Small focal areas of hepatic cell necrosis and inflammatory infiltration associated with parenchymal giant cells have been described by Craig and Landing[24] and by Peace.[25] These later findings seem to be present in the less fulminating cases.[4, 14, 20] It is thought by some that the presence of multinucleated giant cells may be evidence of regeneration; but by others, their presence is considered to be a degenerative phenomenon. It is apparent from the literature that giant cells are not a constant finding in all of the cases being considered as viral hepatitis, possibly originating from intrauterine homologous serum hepatitis infection.

SUMMARY

The history of a family in which the mother, who had had jaundice in adolescence, gave birth to three children, all of whom had jaundice before 2½ months, is reported. The first two children recovered uneventfully, but the third child died. At post-mortem examination evidence of widespread destruction of liver tissue was present. The mother and one of the siblings had positive cephalin flocculation tests. It is questionable whether the mother's jaundice in adolescence or a later serum hepatitis should be correlated with her positive cephalin flocculation test and the transmission of hepatitis to her offspring.

I wish to express my appreciation to Dr. Katharine Dodd, Professor and Head of the Department of Pediatrics of the Arkansas School of Medicine. Her interest and assistance made this paper possible.

REFERENCES

1. Zondek, B., and Bronberg, Y. M.: Infectious Hepatitis in Pregnancy, J. Mt. Sinai Hosp. **14**: 222, 1947.
2. Hsia, D. Y. Y., Taylor, R. G., and Gellis, S. S.: Long-term Follow-up Study on Infectious Hepatitis During Pregnancy, J. PEDIAT. **41**: 213, 1952.
3. Drake, M. E., Barondess, J. A., Bashe, W. J., Jr., Henle, G., Henle, W., Stokes, J. S., Jr., and Pennell, R. B.: Failure of Convalescent Gamma Globulin to Protect Against Homologous Serum Hepatitis, J. A. M. A. **152**: 690, 1953.
4. Stokes, J., Jr., Berk, F. J., Malanut, L. L., Drake, M. E., Barondess, J. A., Bashe, W. J., Wolman, I. J., Farquhar, J. D., Bevan, B., Drummond, R. J., Maycock, W. O'A., Capps, R. B., and Bennett, A. M.: The Carrier State in Viral Hepatitis, J. A. M. A. **154**: 1059, 1954.
5. Gardner, H. T.: History of Viral Hepatitis in Germany, Am. J. Med. **8**: 561, 1950.
6. Turner, R. H., Snavely, J. R., Grossman, E. B., Buchman, R. N., and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation With Yellow Fever Vaccine, Ann. Int. Med. **20**: 193, 1944.
7. Smith, B. F.: Occurrence of Hepatitis in Recently Tattooed Service Personnel, J. A. M. A. **144**: 1076, 1950.
8. Droller, H.: Outbreak of Hepatitis in a Diabetic Clinic, Brit. M. J. **1**: 623, 1944.
9. Cockburn, W. C.: Homologous Serum Hepatitis and Measles Prophylaxis; Report to Medical Research Council, Brit. M. J. **2**: 6, 1951.
10. Porter, J. E., Shapiro, M., Maltby, G. L., Drake, M. E., Barondess, J. A., Bashe, W. J., Jr., Stokes, J., Jr., Oliphant, J. W., Diefenbach, W. C., Murphy, R., and Leone, N. C.: Human Thrombin as a Vehicle of Infection in Homologous Serum Hepatitis, J. A. M. A. **153**: 17, 1953.
11. Davidson, W. C.: Viral Hepatitis and Its Risk From Blood and Plasma Transfusions, J. PEDIAT. **46**: 717, 1955.
12. Gellis, S. S., Craig, J. M., and Hsia, D. Y.: Prolonged Obstructive Jaundice in Infancy, Am. J. Dis. Child. **88**: 285, 1954.
13. Schwarz, M. E., Gilman, R. A., and Schwartz, M.: Neonatal Hepatitis, J. A. M. A. **155**: 557, 1954.
14. Scott, R. B.: Viral Hepatitis in Early Infancy, Pediatrics **13**: 447, 1954.
15. Williams, R. R.: Fulminant Form of Epidemic Hepatitis in a Two-Month-Old Infant, J. PEDIAT. **35**: 244, 1949.
16. Moncrieff, A.: Infection in the Newborn Baby, Brit. M. J. **1**: 1, 1953.

17. Dible, J. H., Hunt, W. E., Pugh, V. W., Steingold, L., and Wood, J. H. F.: Fetal and Neonatal Hepatitis and Its Sequelae, J. Path. & Bact. **67:** 195, 1954.
18. Still, W. J. S.: Familial Hepatic Cirrhosis, Arch. Dis. Childhood **30:** 354, 1955.
19. Ehrlich, J. C., and Ratner, I. M.: Congenital Cirrhosis of the Liver With Kernicterus, Am. J. Path. **31:** 1013, 1955.
20. Krainin, P., and Lapan, B.: Neonatal Hepatitis in Siblings, J. A. M. A. **160:** 937, 1956.
21. Harris, R. C., Anderson, D. H., and Day, D. L.: Obstructive Jaundice in Infants With Normal Biliary Tree, Pediatrics **13:** 293, 1954.
22. Lucke, B.: Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20:** 471, 1944.
23. Wood, D. A., and Block, M. B.: Further Notes on the Pathology of Acute Epidemic Hepatitis and Homologous Serum Jaundice, Am. J. Clin. Path. **16:** 746, 1946.
24. Craig, J. M., and Landing, B. H.: Form of Hepatitis in the Neonatal Period Simulating Biliary Atresia, Arch. Path. **54:** 321, 1952.
25. Peace, R.: Fatal Hepatitis and Cirrhosis in Infancy, Arch. Path. **61:** 107, 1956.
26. Gellis, S. S.: Editor's Comment, Yearbook of Pediatrics, 1954-1955, p. 102.

An Enquiry Into the Nature, Cause, and Cure, of the Angina Suffocativa, &C.

In general, this disease was confined to children under ten years old, though some few grown persons, particularly women (while it prevailed), had symptoms in some respects resembling it. Most of those who had it were observed to droop for several days before they were confined. And the first symptoms, in most instances, were a slightly inflamed and watery eye, a bloated and livid countenance, with a few red eruptions here and there upon the face, and in one case a small ulcer in the nose, whence oosed an ichor so sharp as to inflame and erode the upper lip. At the same time, or very soon after, such as could speak, complained of an uneasy sensation in the throat, but without any great soreness or pain. Upon examining it, the tonsils *or almonds*, appeared swelled and slightly inflamed, with a few white specks upon them, which, in some, increased so as to cover them all over with one general slough, and in a few the swelling was so great, as almost to close up the passage of the throat; but this, altho' a frequent symptom, did not invariably attend the disease; and some had all the other symptoms without it. The breath was either no ways offensive, or had only that kind of smell which is occasioned by worms; and the swallowing was very little, if at all, impeded.

These symptoms, with a slight fever at night, occurred in some for five or six days, without affecting their friends; in others a difficulty of breathing came on within twenty-four hours, especially in the time of sleep, and was often suddenly encreased to so great a degree as to threaten immediate suffocation. In general, however, it came on later, increased more gradually, and was not constant; but the patient would now and then enjoy an interval of an hour or two, in which he breathed with ease, and then again a laborious breathing would ensue, during which he seemed incapable of filling his lungs, as if the air was drawn through a too narrow passage.

SAMUEL BARD, 1771.

COARCTATION OF THE AORTA WITH ANEURYSM AND RUPTURE INTO THE ESOPHAGUS

Report of a Case and Review of the Literature

David Whyte, M.D.,* and Abraham T. Lu, M.D.
Los Angeles, Calif.

COARCTATION of the aorta with aneurysm formation distal to the site of stenosis and rupture into the esophagus with fatal hematemesis is a rare condition. The purpose of this report is to record such a case in a child and briefly review the literature in regard to the frequency of this anomaly.

CASE REPORT

An 8-year-old girl was admitted to the hospital with complaints of nausea, epigastric pain, and hematemesis.

The patient had been a normal, full-term baby, delivered after an uncomplicated pregnancy by spontaneous delivery. The patient had been breast fed for eleven months, then placed on regular table food. The growth and development had followed a normal pattern. The family consisted of eight siblings, as well as parents, and all were living and well.

The patient had been in good health until eight months prior to this admission, when she had been treated for encephalitis and during which hospitalization the diagnosis of coaretation of the aorta was established. Subsequently the parents refused permission for surgical correction of the vascular anomaly and the patient was discharged.

The patient remained well until one week prior to admission, when she was hit on the arm by a baseball, fell down, and left school for the afternoon. At home that evening she refused her supper, and later vomited some blood. The following few days she complained of nausea followed by cramping epigastric pain. Early on the morning of admission the patient vomited some bright red blood.

Physical examination revealed a well-developed, well-nourished Mexican female child who did not appear acutely ill. The pulse rate was 96, respiratory rate 26, rectal temperature 102.6° F., and the blood pressure 165/115 in the left arm and 170/120 in the right arm. Examination of the nose and throat failed to reveal the source of hemorrhage. The neck was supple and there was a visible pulsation at the suprasternal notch and a palpable thrill over both jugular veins. Auscultation of the lungs revealed decreased breath sounds on the left with some inspiratory râles and expiratory wheezes. The right lung was clear. The heart rhythm was regular and there was a grade 1 systolic murmur at the apex and a grade 2 systolic murmur at the left and right second intercostal spaces. The abdominal examination revealed no masses or tenderness. The left elbow joint was tender to palpation and painful on motion. The reflexes were normal.

Laboratory studies gave the following results: hemoglobin 12.7 grams per 100 c.c., hematocrit 37 per cent, leukocytes 17,200 per cubic millimeter, and a normal differential count. The Wassermann test was negative. The

From the Departments of Pediatrics and Pathology, College of Medical Evangelists, School of Medicine.

*Present address: 5840 N. Adenmoor, Lakewood 11, Calif.

voided urine specimen was of turbid appearance, amber color, acid pH, specific gravity 1.022, and contained many pus cells. X-ray of the chest (Fig. 1) revealed a compensatory emphysema of the left upper lobe with atelectasis of the lingula. The heart was prominent but not grossly enlarged. The aortic contour was not diagnostic. There was a waviness of the inferior margins of ribs three through eight, and sclerosis was seen at these minimal notches.

On admission to the hospital, the patient was given intramuscular penicillin and placed at complete bed rest. Within five hours of hospitalization, three episodes of vomiting occurred, but only the last emesis contained blood. The patient was given intravenous fluids and shortly afterward a whole-blood transfusion. The morning following admission the patient was much improved and requested food. She was placed on a liquid diet which was retained. On the evening of the second day, a large black stool was passed. A barium swallow and x-ray study of the upper gastrointestinal tract was ordered for the following morning in an attempt to locate the source of hemorrhage. Early on the third hospital day, the patient awoke and vomited large amounts of blood, which at times seemed to spurt from her mouth. The patient went into shock almost immediately and died within a few minutes.

Fig. 1.—Roentgenogram of the chest showing notching of the ribs and normal-sized heart.

Autopsy.—The body was that of a well-developed, well-nourished Mexican female. There were no gross abnormalities noted on external examination of the body. Except for evidence of old infarcts of the kidneys, the pertinent pathological changes were restricted to the cardiovascular and gastrointestinal systems.

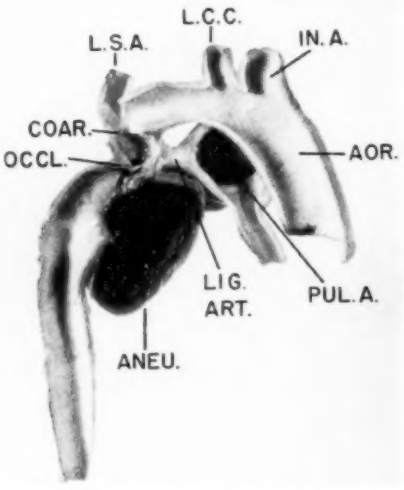


Fig. 2.—Posterior view of sectioned aorta showing the dilated innominate artery (IN.A.), left common carotid (L.C.C.), left subclavian artery (L.S.A.), the coarctation (COAR.) and complete occlusion (OCCL.), distal to which is the aneurysm (ANEU.). The pulmonary artery (PUL.A.) and ligamentum arteriosum (LIG.ART.) are also shown.

The heart was generally hypertrophied, weighing 180 grams (normal is 110 grams). The chambers, valves, interatrial and interventricular septa and coronary arteries showed no developmental abnormalities. The large vessels arising from or returning to the heart showed no abnormalities in relationship. The ductus arteriosus was closed. The ascending aorta measured 1.6 cm. in diameter, the transverse aorta, 1.1 cm. The transverse aorta between the left common carotid and

left subclavian arteries was elongated. The three branches arising from the aortic arch appeared larger than usual, especially the innominate artery which measured 9 mm. in diameter, while the left common carotid and subclavian measured 6 mm. each. The segment between the left subclavian artery and the point of insertion of the ligamentum arteriosum was diffusely narrowed, with complete occlusion at a point just distal to the ligamentum arteriosum.

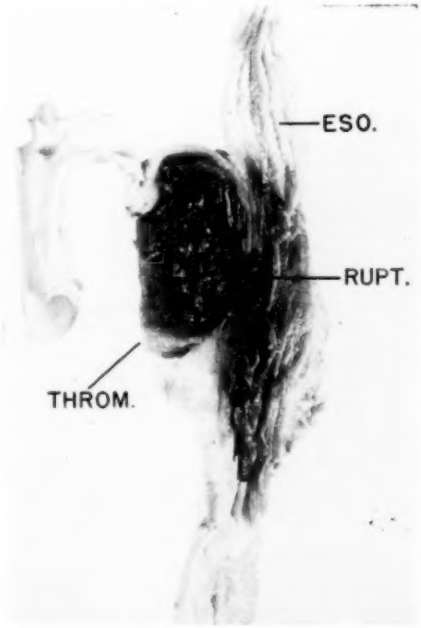


Fig. 3.—This shows the aneurysm filled with thrombus (THROM.) and its adhesion to and rupture (RUPT.) into the esophagus (ESO.).

Immediately distal to the coarctation and occlusion was a 4.5 by 3.5 by 2.5 cm. saccular aneurysm lying inferior, posterior, and to the right of the aorta. The mouth of the aneurysm was oval and measured 1 cm. along the axis of the aorta and 0.6 cm. transversely. The aneurysm was almost completely filled with laminated thrombus. The aneurysm was adherent to the left bronchus, from which it was easily separated, and to the esophagus, where an aortoesophageal fistula had formed. The hemorrhage from the rupture of the aneurysm had dissected the wall of the esophagus for a distance of 6 cm. The site of perforation of the esophagus was below the lower border of the aneurysm. Blood clots were found in the esophagus, stomach, and intestines.

DISCUSSION

In regard to frequency of coarctation of the aorta, Clagett and coworkers[1] estimated on the basis of post-mortem studies that the condition occurs once in every 1,500 to 2,000 individuals. Abbott[2] in her summary of 200 cases stated that localized dilatation of the descending aorta immediately below the stenosis is common. In comparison, however, dilatation of the ascending aorta was much more frequent, occurring in 101 of the 200 cases reported. Similarly, Reifenstein and associates[3] in a report of 104 cases observed that dilatation of the descending aorta was less commonly found.

In a recent report, Holman[4] states that dilatation of the descending aorta beyond a coarctation occurs frequently. According to Ellis and collaborators,[5] however, thoracic aneurysms associated with coarctation more commonly are located distal to the coarctation.

The rupture of a thoracic aneurysm into the esophagus is extremely rare, according to Calenda and Uricchio,[6] only five cases having been described in the past twenty-seven years. Krudy and Smith,[7] however, state in their review of the literature that the incidence of rupture into the esophagus varies from 9.4 to 20.4 per cent. These percentages are based on earlier studies and were, as pointed out, compiled during an era with much higher incidence of syphilitic aneurysms.

In her study, Abbott[2] reported five cases of spontaneous rupture of the descending arch at or near the site of the coaretation. In describing congenital malformations of the heart, Taussig[8] stated that rupture of the aorta usually occurs proximal to the point of coaretation, but has occurred below the constriction in a few cases. In their series, Reifenstein and coworkers[3] described seven cases with rupture distal to the coaretation, including two cases with survival following rupture. Shumacker[9] reports a case of coaretation and aneurysm distal to the stenosis treated by excision and end-to-end anastomosis of the aorta. Recently, Broustet and associates[10] described a case of dissecting aneurysm with rupture of the aorta beyond a coaretation.

Coaretation of the aorta with aneurysm distal to the coaretation and rupture into the esophagus has previously been reported in a 19-year-old female by Bargi.[11] A similar condition was reported by Barsantini and Bazzano[12] in a 24-year-old male, but the aneurysm ruptured into the bronchus as well as the esophagus. Moragues and colleagues[13] described a case in an 11-year-old boy, with coaretation of the aorta and formation of an aneurysm distal to the stenosis, complicated by rupture into the esophagus.

From the foregoing case history and review, it is apparent that this condition is extremely rare, especially in children, the present case representing the second and the youngest child to be found in the literature.

SUMMARY

A case of coaretation of the aorta with aneurysm distal to the stenosis and rupture into the esophagus with fatal hematemesis is presented. The literature concerning coaretation, aneurysm formation distal to the stenosis, and rupture beyond the stenosis is briefly reviewed.

REFERENCES

1. Clagett, O. T., Kirklin, J. W., and Ellis, F. H., Jr.: Surgical Treatment of Coaretation of the Aorta, S. Clin. North America **35:** 937, 1955.
2. Abbott, M. E.: Coaretation of the Aorta of the Adult Type. II. A Statistical Study and Historical Retrospect of 200 Recorded Cases With Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, Am. Heart J. **3:** 392, 574, 1928.
3. Reifenstein, G. H., Levine, S. A., and Gross, R. E.: Coaretation of the Aorta; A Review of 104 Autopsied Cases of the "Adult Type," 2 Years of Age or Older, Am. Heart J. **35:** 146, 1947.
4. Holman, E.: The Obscure Physiology of Poststenotic Dilatation; Its Relation to the Development of Aneurysms, J. Thoracic Surg. **28:** 109, 1954.
5. Ellis, F. H., Jr., Clagett, O. T., and Kirklin, J. W.: Aneurysms of the Aorta, S. Clin. North America **35:** 953, 1955.
6. Calenda, D. G., and Uricchio, J. F.: Gastrointestinal Hemorrhage Due to Rupture of Aortic Aneurysm Into the Esophagus, J. A. M. A. **153:** 548, 1953.
7. Krudy, A. G., and Smith, J. A.: Multiple Saccular Aneurysms of the Thoracic Aorta with Spontaneous Rupture into the Esophagus, Dis. Chest **27:** 690, 1955.
8. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund, p. 482.
9. Shumacker, H. B., Jr.: Coaretation and Aneurysm of the Aorta: Report of a Case Treated by Excision and End-to-End Suture of Aorta, Ann. Surg. **127:** 655, 1948.
10. Broustet, P., Belot, J., Castaing, R., Blanchot, P., Bricaud, H., and Martin, C.: Anevrysme dissequant et rupture de l'aorte en aval d'une coaretation, Arch. mal. coeur **48:** 609, 1955.
11. Bargi, L.: Contribuito allo studio delle stenosi aortiche dellaro, Clin. med. ital. **65:** 152, 1934.
12. Barsantini, J. C., and Bazzano, J. J.: Estenosis del istimo de la aorta, Arch. urug. med., cir. y especialid **13:** 448, 1938.
13. Moragues, V., Moore, L. T., and Rossen, J. A.: Coaretation of the Aorta With Rupture of the Wall Below the Point of Constriction, Am. Heart J. **24:** 828, 1942.

AN EXTRACRANIAL VARIX OF THE SIGMOID SINUS

P. P. Rickham, M.S., F.R.C.S., and Herman W. Lipow, Captain, USAF (MC)
Liverpool, England

ANATOMICAL variations of the lateral and sigmoid sinuses have aroused considerable interest and detailed investigations.[1-5] In spite of this focalized interest, we have been able to find only two previously reported cases of extracranial varices of intradural sinuses in the world literature.

An extracranial varix is probably a rare anomaly, but one that demands correct preoperative diagnosis because of the danger to life during surgery. Of the two previously reported cases, surgical therapy was attempted in only one, and resulted in the death of the patient. Death was probably due to an air embolism, entering the dural sinus through the patent communication exposed during operation. Because of this danger it is thought worth while to call more widespread attention to this entity and to report the first case handled successfully by operation.

CASE REPORT

A. B. was born on March 5, 1955, to a 28-year-old white primigravida, following an uneventful pregnancy. The prenatal serology was negative. Labor began spontaneously. The mother received a saddle block anesthesia. Presentation was cephalic, and position L.O.A. The infant was delivered by low forceps. At birth he weighed 6 pounds 3½ ounces, and was 19 inches in length. Head circumference was 13¼ inches. The immediate neonatal course was uneventful. Physical examination on the first day revealed a marked forceps impression over the right cheek. The superficial skin over the cheek was abraded. This area became crusted and healed rapidly without residual defect. No facial paralysis or other abnormalities were noted.

The mother noted the mass behind the right ear within the first few weeks of life. At 7 weeks of age examination revealed a small mass about 1 cm. in diameter in the right postauricular region. The mass appeared to be a dilated vein and was quite easily compressible. There was no superficial discoloration and it had not the spongy feel of a cavernous hemangioma. With crying, the mass definitely increased in size. None of the superficial veins of the neck or the scalp showed signs of venous distention.

The mass did not appear to increase in size over the next few months and the infant's growth and development progressed very satisfactorily.

Operation.—Surgery was performed by one of us (P. P. R.) on July 29, 1955, at which time the infant was 4½ months of age. At operation under endotracheal gas, oxygen, and ether anesthesia (Dr. A. Stead), a vertical skin incision was made 1 cm. behind the right ear. The mass was found to be composed of a thin-walled sac, about 1 cm. by 0.5 cm. The sac was blackish blue and obviously contained blood. Two small veins entered the posterior surface of the sac and were ligated. A larger, whitish, thick-walled vessel entered the upper aspect of the anterior surface of the sac (Fig. 1).

From the Alder Hey Children's Hospital, Liverpool, England, and the 7559 USAF Hospital, Burtonwood, England.

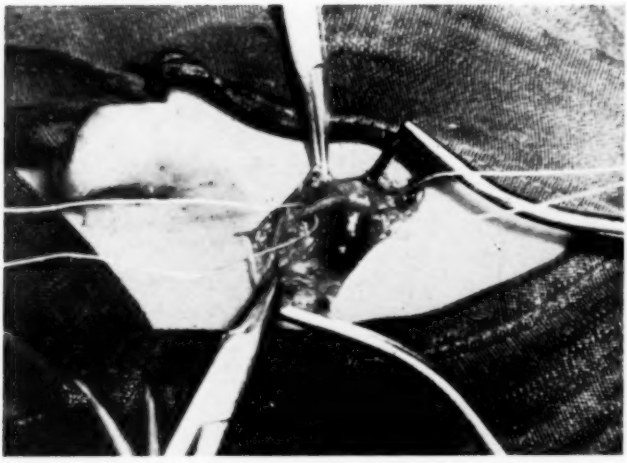


Fig. 1.—Showing the appearance of the varix at operation. A thick-walled vessel is seen at the upper and anterior aspect of the varix.

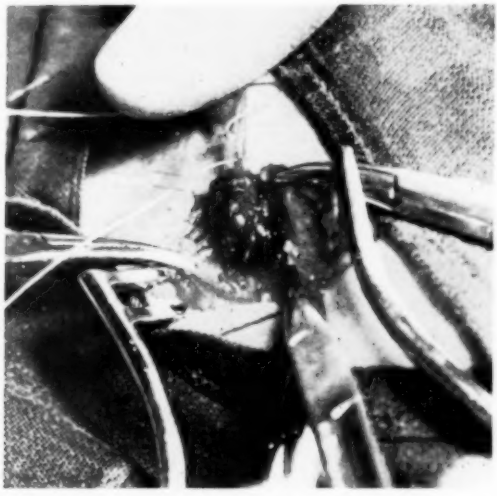


Fig. 2.—The varix has been dissected free and retracted upward. The narrow neck traversing the mastoid bone is now seen.

This vessel, as well as the sac, showed definite pulsation. At the time of operation it was considered that the vessel was an artery and that we had encountered an arteriovenous aneurysm between the posterior auricular artery and the dilated mastoid emissary vein. The vessel was ligated and it was then possible to dissect the aneurysmal sac down to its attachment to the mastoid bone. There the sac narrowed markedly and the neck traversed the periosteum and disappeared through a small hole in the mastoid (Fig. 2). The neck was clamped, transfixed, and ligated with silk. The defect in the bone was about 0.4 cm. in diameter. The wound was closed and the patient made an uneventful recovery.

Pathological Examination.—Examination of the specimen by Dr. E. G. Hall revealed a thick-walled venous sac with a small, friable, pink mass attached to the inner surface of one wall. The greatly thickened vessel entering the sac was found microscopically to be a small, thick-walled vein, and not an artery as was suspected at operation.

The friable mass consisted microscopically of splinterlike anisotropic crystals embedded in loose connective tissue. (The behavior of the crystals to chemical reagents suggested that they consisted of calcium sulfate.) In the surrounding tissue were several small vessels, both arterioles and venules. Several of the arterioles showed fibrinoid necrosis of the wall and obliteration of the lumen, with small areas of hemorrhage and central recanalization. The possible significance of these findings is discussed below.

REVIEW OF LITERATURE

Moreaux[7] in 1929 was probably the first to describe an extracranial ampulla of the lateral sinus. His patient was a girl 23 years of age, with a compressible mass over the right mastoid region. The mass had been present since early childhood, and had shown no disproportionate increase in size over the years. The patient's father, a doctor, had on numerous occasions considered incising the mass, but his daughter had dissuaded him. Moreaux describes the lesion as an elastic, fluctuant swelling, 20 by 30 mm. in size, not attached to the skin, but fixed to the underlying structures. It lay in the osseous gutter of the mastoid bone. At operation an enormous venous ampulla was discovered, with a connection through a large bony defect, or gutter, to the lateral dural sinus. Removal was not attempted and the incision was closed without further treatment. No follow-up data are available.

A very similar lesion was described by O'Connor and associates[8] as a varix of the sigmoid sinus. Their patient was a 5-month-old female infant who presented with a mass over the right posterior occipitomastoid region. The mass was easily compressible, 5 cm. in diameter, and showed considerable enlargement during laughing and crying. There was no indication of a local inflammatory state, and no thrills or bruit was elicited over the area. X-rays of the skull revealed the presence of a bony defect in the right occipital region, adjacent to the mastoid cell. A pneumoencephalogram showed no communication between the cerebral subarachnoid space and the mass.

At surgery the mass was found to stem from a small opening just posterior to the right mastoid process. During removal the neck of the mass was transected and the small circular bony defect was observed. The bony defect was noted to be closed by a shiny, valvelike membrane, which apparently kept blood from egressing

from the sigmoid sinus to the varix. On depressing the membrane the blood was seen to issue forth from the sigmoid sinus, but upon releasing the membrane the valvelike action was again noted and blood ceased flowing. During the process of repairing the defect, respirations became labored and the infant died soon afterward. At post-mortem examination the operative findings were confirmed, and the presence of many small bubbles in the vessels over the cerebral hemispheres was taken to be evidence of air embolism. No other abnormalities were found. It was felt by the authors that, during the course of surgical manipulation of the valvelike membrane in the wall of the sinus, air probably entered the circulation in quantities sufficient to cause death.

DISCUSSION

Any patent communication between a dural sinus and a superficial venous lesion obviously assumes great importance when the superficial lesion may be opened during surgery. Although the exact cause of death in the patient reported by O'Connor and co-workers[8] was not definitely established, the evidence suggests that air embolism did occur. Their report was published at the time we were about to operate on our patient, and we gratefully acknowledge being alerted to the probable diagnosis and possible complications by their timely report.

The possibility that this danger exists in all cases of extracranial varices is inescapable. Great care, therefore, should be taken in operating on any postauricular mass thought to be a misplaced varicose vein or minor vascular anomaly.

The two previously reported cases do not mention the time at which the mass was first noted. In ours the mother noted the mass within the first few weeks of life. It was not noted in the course of the nursery examinations, but as it was not specifically looked for, it seems quite possible that it may have been present at the time of birth.

Both earlier reports suggested that the varix probably represented a congenital malformation. Moreaux[7] considered two possible etiological mechanisms. The defect could be primarily and entirely a vascular malformation, occurring at the time of the formation of the cranial venous sinuses, or the venous anomaly might be secondary to some underlying defect in the formation of the mastoid bone. He favored this latter possibility, and pointed out that Poirier had shown that the mastoid bone was formed by the union of two primitive ossification centers. He suggested that partial arrest of the bony development might produce a gutter in the bone and thus affect the developing venous system.

The normal embryological development of the intracranial venous sinuses was well described by Streeter.[2] He described the various mechanisms by which the three pair of primitive venous plexuses drained by the "head vein" gradually evolve the dural sinuses and cerebral venous system.

O'Connor and associates[8] felt the varix in their patient could best be explained by failure of obliteration of portions of the posterior plexus, which in the 50 mm. embryo is connected with the sinus at a point near the entrance of the mastoid vein. They felt the incomplete closure of this communication resulted in a shutter valve effect permitting periodic ingress of

blood into the sac, thereby maintaining it as an anatomical structure, whereas, if complete closure had occurred, the venous network would have become obliterated in the manner of other embryological venous channels.

In our case no valvelike membrane was detected but the possibility of its existence cannot be definitely excluded, as the penetrating pedicle was clamped before being transected and sutured, in a purposeful attempt to prevent air embolism.

The finding of the thickened vessel wall, containing crystals on the inner lining, and a necrotizing arteriolitis in the arterioles of the surrounding tissues suggests the possibility that trauma may have occurred in this area. It is to be recalled that the infant was delivered by low forceps, and that a forceps mark with superficial abrasion of the skin over the right cheek was noted immediately after birth. That trauma to the region behind the ear occurred during the delivery cannot be stated with certainty, but the possibility that the forceps blades might exert pressure in this area seems reasonable.

Although it is true that a varix existing at the time of delivery would be more prone to injury than a normal-sized postauricular vein, one cannot help but speculate on the possibility that a normal postauricular vein might become varicose following forceps trauma during delivery. We find it difficult to postulate an adequate physiological mechanism to explain the dilatation of the injured vessel. If such simple trauma were the determining factor, one would expect to encounter the entity with much greater frequency than has been reported to date.

No details concerning the delivery are available in the two previously reported cases. In view of the unusual pathological findings in this case, it seems worth while to make specific note of any possible source of trauma to this area in future cases.

SUMMARY

The successful surgical repair of an extracranial varix of the sigmoid sinus in an infant is reported. The potential danger of air embolism during surgical removal of these varicosities is stressed. The two previously reported cases are reviewed, and possible etiologies are discussed.

REFERENCES

1. Waltner, J. G.: Anatomic Variations of the Lateral and Sigmoid Sinuses, Arch. Otolaryng. **39**: 307, 1944.
2. Streeter, G. L.: Development of Venous Sinuses of Dura Mater in Human Embryo, Am. J. Anat. **18**: 145, 1915.
3. Knott, J. F.: J. Anat. & Physiol. **16**: 27, 1881.
4. Hoople, G. D.: Ann. Otol., Rhin., & Laryng. **45**: 1019, 1936.
5. Coudert, R.: Anatomie et pathologie de la veine emissaire mastoidienne, Theses, Paris, No. 492, 1900.
6. Wood, T. B.: Anatomical Variations in the Lateral Sinus and Its Tributaries, M. Times, New York **67**: 270, 1939.
7. Moreaux, R.: Sinus lateral ampullaire extracranien, Ann. mal. oreille, larynx, **49**: 732, 1929.
8. O'Connor, W. J., Cook, A. W., and Bedo, A. W.: Varix of the Sigmoid Sinus, Pediatrics **15**: 768, 1955.

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

AT 6 weeks of age, this male infant was first seen in The Children's Medical Center, medical outpatient department, for study of cardiac disease. He was the product of the second pregnancy of a 35-year-old mother. Delivery was at term after a completely normal gestation without maternal illness.

The family history revealed diabetes, cancer, and question of rheumatic fever in grandparents.

He had overt cyanosis at birth and was kept in oxygen for four days. On the second day of life, a heart murmur and dextrocardia were noted. He went home from the hospital at age 6 days with cyanosis still present and exaggerated by crying. He fed well and gained on a standard formula. When first examined here, he was a well-developed, well-nourished cyanotic infant whose blood pressure was 64 in the arm and 68 in the leg. The heart was on the right. It had a regular sinus rhythm of 96. A grade III systolic murmur was heard transmitting to the right axilla. There was clubbing of the fingers and toes. No edema or liver enlargement was noted. Electrocardiogram showed right ventricular hypertrophy. Fluoroscopy revealed diminished pulmonary vasculature, right ventricular enlargement, and a generally abnormal configuration with no identifiable pulmonary artery segment.

Over the succeeding two and one-half years he was seen regularly in the Cardiac Clinic. Subsequent x-ray studies revealed situs inversus of the abdominal viscera. He grew well, with his height and weight falling along the seventy-fifth percentile. He had poor exercise tolerance, and his motor development was slow. A right chest deformity developed. At age 1½ years a diastolic murmur was first noted at the apex. At age 1 year 8 months he began to have "limp spells" after crying, and frequent nocturnal crying spells. At age 2 years he could walk only with support and was saying about a dozen words.

His only hospital admission was at age 2½ years. Three weeks prior to that he had an upper respiratory infection which cleared without treatment in three or four days. He remained irritable subsequently, and one week prior to admission his abdomen was noticeably distended. Over the succeeding day he became drowsy and

developed periorbital edema and dyspnea. When seen by his physician he was referred to The Children's Medical Center with congestive heart failure.

Physical examination disclosed an edematous, cyanotic child in mild distress, with temperature 99.8° F., pulse 108, respirations 40, blood pressure 114/94 (arm) and 126/94 (leg). Abnormal findings included an edematous facies, hypertelorism, equal right and left chest prominence, dull lung bases with bilateral râles, a cardiac impulse at the right lower sternal border with the apex 9 cm. to right of midsternal line. A grade III rough systolic murmur was heard at the second left intercostal space and transmitted to back and neck; a grade II blowing diastolic murmur was found at the right lower sternal border, and a grade III harsh systolic murmur at the apex, transmitted to the axilla and back. A gallop rhythm was present. Hepatomegaly of 6 cm. below the right costal margin and 2 cm. below the left costal margin was noted. Clubbed toes and fingers and swollen feet were found.

Laboratory data included a urine showing 2 plus proteinuria, hemoglobin 15 grams, white blood count 10,400, with 65 per cent polymorphonuclear cells; nonprotein nitrogen 47.2 mg. per cent; negative nose and throat cultures, and a venous pressure of 210 mm. of water. An x-ray film of the chest showed a greatly increased heart size. Electrocardiogram showed dextrocardia and auricular hypertrophy.

The child was digitalized (initially with Cedilanid and later with digitoxin), given two mercurials, and placed on penicillin and Gantrisin. He was put in oxygen and given morphine p.r.n. One observer (a cardiologist) heard a pericardial friction rub. On his therapeutic regimen he improved over the next four days, with clearing of his chronic heart failure. He then spiked a fever to 103° F., and was found to have bilateral otitis media which cleared in three more days. He received gamma globulin for measles exposure. With his improvement, he was considered well enough to undergo cardiac catheterization. This showed evidence of pulmonary stenosis of a valvular type, with right to left shunt likely at the atrial level. One week after catheterization, mild modified measles developed, with a temperature never over 101° F. He was seen by a surgical consultant who agreed that a pulmonary valvulotomy (Brock) might help him. Because of persisting fever (100 to 101° F.) attributed to his ear infections, he was sent home on Gantrisin, to return in three weeks for operation. Two weeks after discharge he died at home.

DISCUSSION

DR. SIDNEY FARBER.—Dr. Abraham M. Rudolph* will begin the discussion.

DR. ABRAHAM M. RUDOLPH.—This child is one who obviously had congenital heart disease; I say that because he had cyanosis with a heart murmur from birth. We are not told how much cyanosis he had, but from the fact that he had clubbing at the age of 6 weeks, I must presume that this is a fairly severe cyanosis. If we have cyanosis on the basis of congenital heart disease, we must assume that there is a shunting of venous blood from the right to the left side of the heart. This shunting of blood could occur at several different levels of the

*Dr. Abraham M. Rudolph is Assistant Cardiologist, Children's Hospital.

heart. First of all, it may occur through an atrial septal defect; second, it may occur at the ventricular level through a hole in the ventricular septum; or third, it may occur if there is a partially or completely transposed aorta. With a simple auricular or ventricular septal defect cyanosis is not present, because the pressure differentials in the heart are such that no significant amounts of blood would shunt from the right to the left. So we must say, then, that if this child had an auricular or ventricular septal defect through which shunting of blood was occurring, it must be a complicated lesion, and the complicating lesion must be one that will increase the pressure in the right side of the heart. If this shunting is at the atrial level, then we could say that this may be due to one of three things: an associated obstruction of the tricuspid valve region, such as in tricuspid atresia or stenosis; an obstruction at the right ventricular level, due to pulmonary stenosis; or an obstruction in the lungs such as obstructive pulmonary vascular disease. The same consideration would be pertinent with ventricular septal defect; there would have to be an associated pulmonary stenosis or obstruction in the lungs to cause cyanosis. Finally, with an overriding aorta, either tetralogy of Fallot or transposition of the aorta could give cyanosis.

The next factor of quite considerable importance in this child is that he grew well, with a height and weight in the seventy-fifth percentile. That indicates that this child was getting a fairly good supply of oxygen to the tissues, and must have had a fairly good systemic blood flow. He could not have had a marked unsaturation of arterial blood, since if the saturation of the arterial blood is much below 50 per cent, the development is not usually good. This also indicates that there probably was not complete transposition of the great vessels, since in this condition development is usually poor.

This child had a murmur; in the presence of dextrocardia it is extremely difficult to assess murmurs and heart sounds, but from the description a stenotic type of murmur, which would fit with either a pulmonary stenosis or aortic stenosis, is suggested. Other examinations that would help us here would be, first, the x-ray which would tell us if the pulmonary vasculature was increased or decreased, and, second, the electrocardiogram. I do not think I am capable, in the presence of dextrocardia, of determining definitely whether there was right or left ventricular hypertrophy in the electrocardiogram. In this first electrocardiographic tracing, however, at 6 weeks of age, there was no significant auricular hypertrophy, so that the auricular hypertrophy described at a later date could be on a different basis. The impression has always been given that in isolated dextrocardia, without situs inversus, there is usually a complicated cardiac anomaly, but that with dextrocardia in association with complete situs inversus there is usually no significant cardiac anomaly. However, Dr. Helen Taussig[1] clearly states that this is not so, and I am sure that her experience has been confirmed by others. But we can say that when there is dextrocardia and marked cyanosis, the lesion is not usually a simple one. There is no mention in the roentgen interpretation of the position of the aorta. If the aorta was on the right side, as is expected with a dextrocardia,

that position would be compatible with any of the diagnoses mentioned thus far. In true dextrocardia, the ventricles are dextroposed, and present a mirror-image position to the normally placed aorta and pulmonary artery. Therefore, this situation is the same as would arise with a right aortic arch and a normal position of the ventricles. If the aorta was on the left, I would say that this child must have some anomaly of the great vessels.

Could we see the x-ray films, please?

DR. MARTIN H. WITTENBORG.—It is clear that this child has definite situs inversus. The major portion of the cardiac silhouette is projected to the right of the spine, the stomach is on the right and the liver is on the left. I think the striking thing is that the caliber of the pulmonary vessels is definitely diminished, which would suggest diminished pulmonary blood flow. The heart is definitely enlarged and has a globular shape, which suggests, as a rule, right ventricular dilatation. The one exception to this is tricuspid atresia, in which one ventricle practically makes up the whole heart. The main pulmonary artery was not visualized, Dr. Rudolph, which suggests that it is hypoplastic, absent, or abnormally placed. The aortic arch appears to lie on the left, and descend on the left, so that it would be in the contralateral position and, thus, the equivalent of a right aortic arch in a normally placed heart. I had the impression that the right auricle was prominent. Two years later there is a progression of the abnormality of the contour. The heart not only grows in size, relative to the child, but the contour is increasingly globular and the diminished caliber of the pulmonary vessels more striking.

DR. RUDOLPH.—We have confirmatory evidence that this child has a decreased pulmonary blood flow, which suggests pulmonary stenosis. This particular syndrome, of dextrocardia, pulmonary stenosis, left aortic arch, left descending aorta in association with a large ventricular septal defect and auricular septal defect, and a functionally or anatomically bilocular heart, has been described previously.

This child was admitted to the hospital at the age of 2½ years with all the evidences of congestive heart failure, and this seems to have come on fairly acutely. He had an infection that occurred about three weeks prior to the episode of failure, and the question is: why did he develop congestive heart failure? First of all, we have a child who has a tremendous amount of work being done by the heart. The pressure work against the obstruction at the pulmonary valve region and the maintenance of a very good systemic flow demand that the heart must develop hypertrophy and probably dilatation. Any excessive strain on that heart might well induce heart failure. The stress may be a severe infection, due to the increased cardiac output produced by fever and increased metabolism. One of the things that we have to consider is whether this failure was chronic, developing gradually, and that it just became manifest at the time of the infection. If we consider this possibility of chronic failure which manifests itself at this point, then we should consider that the child may have had a pulmonary stenosis with an intact ventricular septum, for such a heart may go into failure with

a large atrium and a high venous pressure. However, with the dextrocardia and left aortic arch, I would assume that there was an anomaly of the great vessels and a ventricular septal defect, and that infection of some sort precipitated the failure. A pericardial friction rub was heard by one observer, a cardiologist; I presume that the parentheses around "a cardiologist" suggest that this was definitely so. I will take the bait, and say this indicated pericarditis. It could be, too, purely and simply infectious pericarditis. However, the child had no significant fever at that time.

Another possibility is that this child had rheumatic fever. I think that, even though the incidence of rheumatic fever is increased in children with congenital heart disease, I would hesitate to make that diagnosis because of the age and the whole course of illness. I would rather suggest that this was just a respiratory infection that had precipitated this child's attack of failure.

The cardiac catheterization gave evidence of pulmonary stenosis of a valvular type with a right-to-left shunt likely at the atrial level. The brachial arterial oxygen saturation was only slightly higher than the right auricular and right ventricular saturation. This means that most of the blood getting through to the systemic system was not much more oxygenated than blood from the right auricle, suggesting a common atrial chamber. Further, the identity of systolic pressures in the right ventricle and systemic artery suggests that there was a functionally single ventricle.

To sum up, I would like to say that this child had dextrocardia with complete situs inversus, pulmonary stenosis at the valvular level, of severe degree, left aortic arch and left descending aorta, ventricular septal defect and atrial septal defect, as either a bilocular heart or perhaps an atrioventricularis communis, and evidence of congestive heart failure.

DR. FARBER.—Thank you, Dr. Rudolph. Dr. Nadas, will you continue the discussion?

DR. ALEXANDER NADAS.—We maintain, and I think we maintain rightly, that if one has a patient with pulmonary stenosis who has a ventricular septal defect in the complex of tetralogy of Fallot, he does not go into congestive failure within the childhood period. He may fail at age 20, 30, or 40, but does not go into congestive failure as early as this child. We have not seen an exception yet. The right ventricular pressure can never rise significantly above systemic arterial pressure in such cases, and early failure does not occur. If this patient's heart did in fact fail as early as this, one has to assume that the ventricular septum was intact. If the ventricular septum was open, then one would have to assume the presence of an infection more debilitating than an otitis media or ordinary respiratory infection. There must be something more basic, such as bacterial endocarditis or rheumatic fever, giving an added load, to put a patient with a pulmonary stenosis and an open ventricular septum into congestive failure.

The other point that I would like to mention is the presence of the friction rub—obviously I am quoted about it—and no one else heard it, or it would not have been said in such a pointed fashion. If pericarditis was present, then bacterial endocarditis can be dismissed because bacterial endocarditis

does not, by and large, give pericardial friction rubs; this would make the rheumatic fever more likely.

One final point concerns this systolic murmur at the second left interspace, which is the place one hears the murmur of pulmonic stenosis if there is no dextrocardia. If there is dextrocardia, the murmur of a stenotic pulmonary valve should be heard at the second right interspace. May not this mean that perhaps a transposition of the great vessels, of some sort, may have been present to bring this about?

DR. JOHN CRAIG.—Would you rule out rheumatic fever because of the age?

DR. NADAS.—I would not. We have seen such cases; but I think they are very rare. Is rheumatic heart disease more common in children with congenital heart disease? I think it is more common. We have cases that hemodynamically do not have lesions that cause congestive failure, such as a small ventricular defect, a small atrial defect, without significant shunt, and yet failure. In those, one may find a high antistreptolysin titer. Those patients are put to bed, given aspirin and, to some, cortisone. They recover and follow the normal course expected from their original anatomic or hemodynamic situation. We say that, possibly, this is a rheumatic process.

DR. CRAIG.—Did this child run a fever when he went home?

DR. SAMUEL KATZ.—We have no record of what happened after he went home. He was discharged with low-grade fever still present. He was kept on Gantrisin during his entire hospital course, almost a month, and was sent home on Gantrisin.

One point of Dr. Rudolph's question that we can add a little light to is that, when he was seen in the Cardiac Clinic, sixty days before admission to the hospital, there was no evidence of failure. He was seen by his private physician at the time of the upper respiratory infection, three weeks prior to our history of failure, and he had no evidence of failure at that time. When he was seen three weeks after this upper respiratory infection, he had evidence of failure. So with competent observation there was no evidence certainly of congestive failure at any time before the upper respiratory infection. He had otitis media at that time, but has had no evidence of it on several checks thereafter. Yet he still ran a fever, even when he left the hospital.

DR. FARBER.—Did anyone in addition to Dr. Nadas hear this friction rub?

DR. KATZ.—The friction rub was heard by several people, but Dr. Nadas heard it first.

DR. FARBER.—Dr. Bernstein, will you present the post-mortem findings?

DR. JAY BERNSTEIN.—The findings in this case were extremely complicated, but they could be characterized as dextrocardia in association with atrioventricularis communis, infundibular and valvular pulmonic stenosis. The heart was greatly enlarged, weighing 350 grams, in comparison with a normal weight of 60 grams, and it extended in situ to the right axillary line. The venae cavae entered a chamber which was on the left but which had in mirror-image the configuration of the right atrium (Fig. 1). A large defect was present at the base of the interatrial septum and was continuous

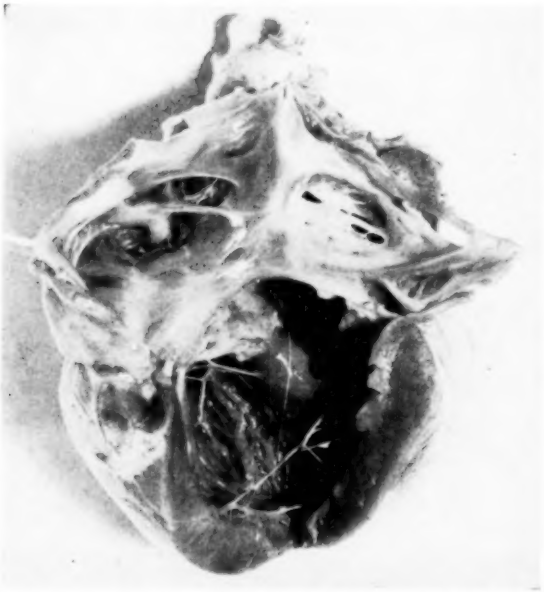


Fig. 1.—The heart is opened from the left side. The atria are transposed and the fossa ovalis on the left has the configuration of that of the normal right atrium. There is a large defect in atrial and ventricular systems. A common atrioventricular canal is present.

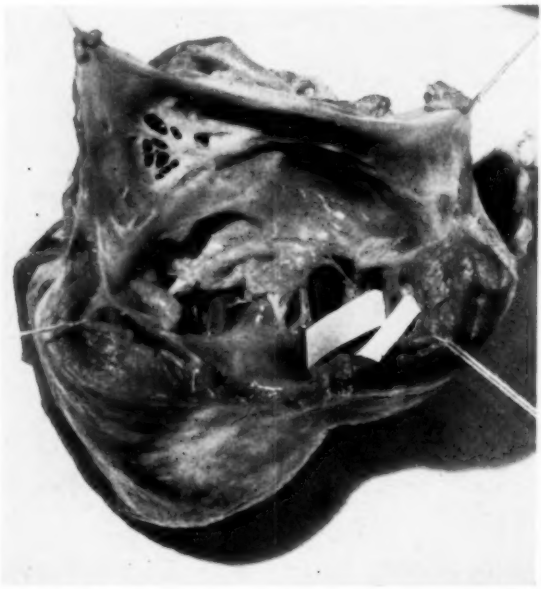


Fig. 2.—The right side of the heart is opened. The fenestrated foramen ovale and the exposed atrium have the configuration of a normal left atrium. The aortic and pulmonary outflow tracts are indicated by the paper arrows. The aorta is transposed but the ventricles are in situs solitus.

with a defect in the interventricular septum, thereby forming a common atrioventricular canal. The valvulus foraminis ovalis was also fenestrated, adding a relatively minor defect within the interatrial septum. The ventricle corresponding to the functionally right atrium had the anatomic configuration of the left ventricle; there was, however, no outflow tract from this ventricle. The pulmonary veins entered an anatomically left atrium although it was actually situated on the right side, and its corresponding ventricle had the general configuration of the right ventricle. There was a single atrioventricular valve in which the leaflets and chordae tendineae were thickened. Both the aorta and the pulmonary artery arose from the right ventricle; the latter was smaller than normal and situated posteriorly to the aorta (Fig. 2). The ductus arteriosus was closed, and the only entrance to the pulmonary artery was through a stenotic infundibulum and valve. Of additional interest were several areas of thickening and fibrosis of the epicardium.

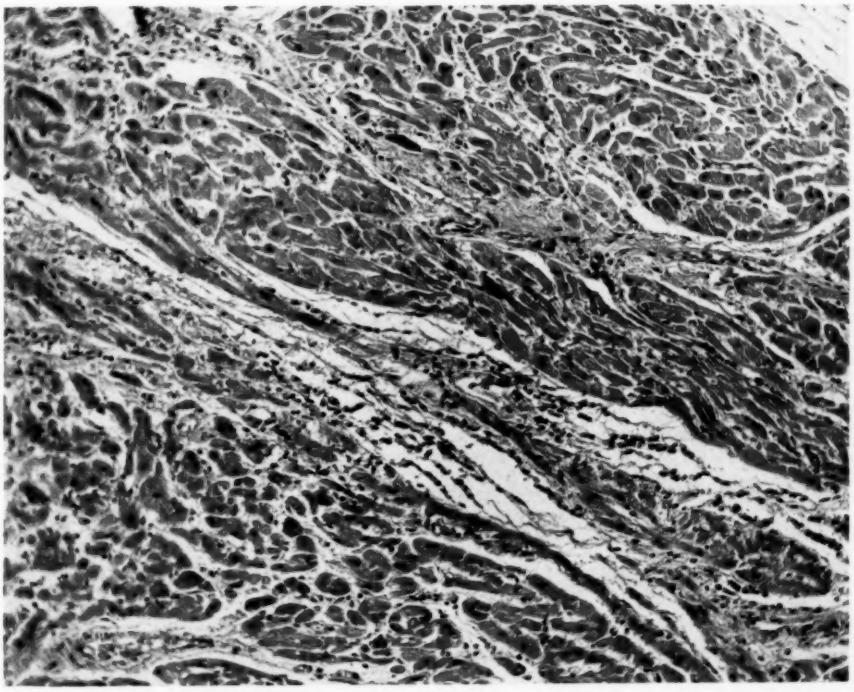


Fig. 3.—Microphotograph, heart. The ventricular myocardium has an infiltrate of chronic inflammatory cells, histiocytes, and occasional Aschoff cells, in a perivascular distribution. (Hematoxylin and eosin; ×130.)

Within the myocardium there was an interstitial infiltrate, which was located predominantly around blood vessels. There was no actual necrosis or fibrinoid degeneration, but the infiltrate consisted of chronic inflammatory cells, histiocytes, myocytes, and

occasional Aschoff cells (Fig. 3). The infiltrate formed perivascular aggregates and involved the epicardium and endocardium, thereby justifying our diagnosis of rheumatic carditis.

In considering the diagnosis of situs inversus in this case, we noted that the usual pulmonary lobation was reversed, but our examination was restricted to the thoracic cavity. Despite the roentgenographic evidence of abdominal situs inversus, we cannot classify this case as one of complete visceral inversion because of the left aortic arch and situs solitus of the ventricles. On reviewing the cases of situs inversus in our files, it became apparent that we do not have any cases of complete visceral inversion in association with dextrocardia, indicating that serious congenital heart disease is not often part of that syndrome. However, there are fifteen cases of partial inversion, twelve of which had no spleen. If we consider the twelve cases of "absent-spleen syndrome," we find that all had serious congenital heart disease (Table I). Of them, eight had anomalous pulmonary venous drainage, and in six cases there was pulmonary stenosis or atresia. There are only three cases of cardiac dextroposition (including the present one), two of them associated with situs solitus of the abdominal viscera. Also, of the twelve cases, there were five of complete abdominal situs inversus, all of which were associated with levoposition of the heart. And of the original fifteen, in the three cases that did have spleens, all had complete abdominal situs inversus in association with levoposition of the heart. It would therefore seem that the situs of either the heart or the abdominal viscera has to be reversed, unless both are normal, for this relationship to hold. Associated abnormalities of the other viscera in the partial inversion syndrome, including the absent-spleen variant, are intestinal malattachment and malrotation, a ventral or common mesentery, asymmetry of the liver, and abnormal pulmonary lobation.

In extrapolating these data to this case, and considering the radiologic

Table I. Syndrome of Partial Visceral Inversion

TOTAL CASES			15
I. Spleen absent			12
Congenital heart disease		12	
Common atrioventricular canal	10		
Anomalous pulmonary venous drainage		8	
Pulmonic stenosis or atresia		6	
Cardiac dextroposition		2	
With abdominal situs solitus	2		
With right aortic arch	1		
Cardiac levoposition		10	
With abdominal situs inversus	5		
With right aortic arch	6		
II. Spleen present			3
Congenital heart disease (all complicated; none with common atrioventricular canal)		3	
Anomalous pulmonary venous drainage		2	
Pulmonic stenosis or atresia		1	
Cardiac levoposition		3	
With abdominal situs inversus	3		
With right aortic arch	0		

findings, we would expect to find abdominal situs inversus, intestinal malrotation and lack of attachment, and an 80 per cent chance of a missing spleen.

DR. FARBER.—Thank you, Dr. Bernstein. Dr. Rudolph, would you like the last word?

DR. RUDOLPH.—I would just like to ask Dr. Bernstein one thing about the classification that he has presented here. The literature has several reports of a well-described syndrome, in which there is a partial, sometimes complete, subdiaphragmatic situs inversus with an absent spleen, with the heart on the left side, and in that particular set of circumstances there are often associated anomalies of the great vessels with ventricular septal defect or atrioventricular communis, and I was just wondering how he was classifying these cases that he presented here. He has both dextrocardia and levocardia, and I wonder whether he has cases of dextrocardia with subdiaphragmatic situs inversus with an absent spleen, and whether he thinks those would fall into a similar group as those with levocardia.

DR. BERNSTEIN.—Including this case, we now have three cases of dextroposition of the heart, and in two of those the abdominal viscera are in their normal situs; in the other there is only partial dextrocardia. On the other hand, with situs inversus of the abdominal viscera we have several cases that have levocardia. The cases form an interrelated group and are classified together, but in none is the visceral inversion complete. For those who are interested, Dr. Biorn Ivemark[2] has recently published a monograph on the problems of splenic agenesis and cardiac anomalies, which draws generously on the material from the Children's Hospital.

REFERENCES

1. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.
2. Ivemark, B. I.: Implications of Agenesis of the Spleen on the Pathogenesis of Cono-Truncus Anomalies in Childhood, Acta paediat., Supp. 104, vol. 44, 1955.

Medical Progress

RECENT DISCOVERIES IN THE ETIOLOGY OF ACUTE RESPIRATORY INFECTIONS: THE ADENOVIRUSES

ROBERT WARD, M.D.
NEW YORK, N. Y.

FOR many years the term "virus" has been bandied about and loosely applied to miscellaneous respiratory and "grippelike" infections which did not behave like bacterial infections, but whose etiology was really in the dark. Lay friends' questions: "What is 'Virus'?" or "What is 'Virus X'?" were not always easy to answer. The only respiratory viruses known until recently, influenza A and B, psittacosis, and Q fever if one included rickettsiae, accounted for but a small fraction of nonbacterial respiratory infections. The remaining illnesses, *presumably* caused by viruses, were known by various names, such as rhinopharyngitis, the common cold, pharyngitis, laryngitis, tracheitis, bronchitis, grippe, febrile catarrh, virus pneumonia, and so forth. Such terms merely describe the site of the most prominent clinical manifestations. It is generally appreciated, however, that different agents may give rise to clinically indistinguishable illnesses. Infection with the same virus, conversely, may yield different clinical pictures in different hosts. It is obvious that an etiological classification of acute respiratory infections would be most welcome.

Now the curtain has been lifted, revealing at least a segment of this unexplored territory. In the last two to three years, a family of related viruses which possess some very interesting properties has been discovered. This family has been known variously as the APC, AD, ARD, and RI viruses—all very confusing, as nomenclature is likely to be at the opening of a new field. Table I is designed to clarify, in part, this confusion. A committee[18] of investigators in this field has recently agreed on the term "adenovirus" to replace those listed above. This will be used in the present review except when the original terms will be used for historical purposes.

The field was opened in 1953 by the back gate, so to speak, by Rowe and his associates.[1] These investigators took bits of adenoids surgically removed from normal children and cultivated them in tissue culture. Sheets of epithelial cells grew out from the original fragments. After eight to twenty-eight days these epithelial cells

From the Department of Pediatrics, New York University College of Medicine, and the Children's Medical Service, Bellevue Hospital.

began to round up and form clumps, and this progressed to complete degeneration. The fluids from these cultures were passed to fresh cultures of adenoids, to human embryonic tissue, and to a strain of human cancer cells known as HeLa. Similar degeneration of the cells was observed and the agent was carried thus through many serial passages. It always produced characteristic cytopathic changes in tissue-culture cells. It did not grow in ordinary bacteriological media. It was destroyed by heating at 62° C. for thirty minutes. It was filtrable; it survived freezing and thawing. It produced no recognizable disease in eggs, suckling and adult mice, suckling hamsters, guinea pigs, rabbits, monkeys, and a chimpanzee. Immunization of rabbits with the tissue-culture fluids containing the agent resulted in serum antibodies capable of neutralizing the agent in tissue culture. Immunization with control culture fluid did not. In other words, the agent showed many of the properties of viruses or rickettsiae. The discoverers first called it the "adenoid degeneration agent" or "AD agent." Although this original approach excited more than a little interest, it should be stressed that at this point there was *no evidence that the AD agent or virus was related to human disease.* It appeared to be a latent virus, "unmasked" by being separated from man and cultivated in tissue cultures.

TABLE I. NEW RESPIRATORY VIRUSES, TERMINOLOGY AND RELATION TO DISEASE

DESIGNATION ACCORDING TO INVESTIGATOR			COMMITTEE ON NOMENCLATURE[18]	CLINICAL PICTURE	SOURCE OF VIRUS
HUEBNER	HILLEMAN	GINSBERG			
[a]APC Ty 1	Latent Ty 1	AD 1	Adenovirus 1	Febrile pharyngitis in children	Adenoids, tonsils, NPH secretions
APC Ty 2	Latent Ty 2	AD 2	Adenovirus 2	Febrile pharyngitis in children [c]PCF	Adenoids, tonsils, NPH secretions
APC Ty 3	[b]RI gp. C	AD 3	Adenovirus 3	PCF, U.R.I., Neva's exanthem	Anal swabs, conjunctival and NPH secretions
APC Ty 4	RI gp. A RI-67	AD 4, ARD	Adenovirus 4	[d]ARD, [e]PAP, "bronchitis"	Throat washings, adenoids
APC Ty 5	Latent Ty 5	AD 5	Adenovirus 5	Febrile pharyngitis in children	Adenoids, tonsils, NPH secretions
APC Ty 6	Latent Ty 6	AD 6	Adenovirus 6	PCF	Adenoids, tonsils, NPH secretions
APC Ty 7	RI gp. B	AD 7	Adenovirus 7	ARD, PAP	Throat washings
APC Ty 8		AD 8	Adenovirus 8	[f]EKC	Conjunctival and corneal scrapings

[a]APC: adenoidal-pharyngeal-conjunctival.
[b]RI: respiratory illness.
[c]PCF: pharyngoconjunctival fever.
[d]ARD: acute respiratory disease.
[e]PAP: primary atypical pneumonia.
[f]EKC: epidemic keratoconjunctivitis.

Proof of a causal relationship to disease in man was not long in coming. Hilleman and Werner,[2] working independently of Rowe and his group, reported in 1954 the isolation of several strains of cytopathogenic agents from soldiers with acute respiratory infections at Ft. Leonard Wood in Missouri during the winter of 1952-1953. Most of the patients had an illness known as "ARD," acute respiratory disease. This was an acute febrile respiratory infection of short duration with both constitutional and local respiratory symptoms. It was characterized mainly by cough and hoarseness. In addition, irritated throat, nasal obstruction, and chest pain were frequent complaints. The incubation period was five to six days. Some of the patients from whom agents were isolated had pulmonary infiltration and were considered to have *primary atypical pneumonia* (PAP). No cold agglutinins or streptococcus MG agglutinins developed in the latter patients. Most of them had a rise in neutralizing antibodies against one of the strains isolated, the RI-67 strain. Later it was shown that the RI-67 strain was indistinguishable from AD type 4 isolated by Rowe and co-workers.[3]

Huebner and his associates[4] reported in 1954 that their many AD strains were found to fall into six distinct serological types. This was done by producing immune serum in rabbits injected with various strains. Neutralizing antibodies were demonstrated against the homologous and related strains, but none against heterologous or unrelated strains. In contrast to the *type specificity* of the neutralization test, it was found that complement-fixing (CF) antigens and antibodies were shared in common by most members of the family. In other words, the CF test revealed general crossing between types, or *group specificity*. The practical importance of the CF test in a screening survey is obvious. Once having found CF antibody, one could then employ the neutralization test to determine the specific type involved.

Parrott and others[5] investigated an outbreak in February, 1954, affecting four patients and four hospital staff members with a febrile illness having the following characteristics: fever up to 104° F., pharyngitis, rhinitis, cervical lymphadenitis, and conjunctivitis. Three had transitory liver enlargement, accompanied by tenderness in two. AD virus, type 3, was detected in six patients. In five it was isolated from swabs of the nasopharynx, and in one from the conjunctival swab. Most of the eight patients showed both CF and neutralizing antibody rises. The occurrence of pharyngitis and conjunctivitis in patients from whom these viruses were recovered, and clean-cut evidence of antibody response in convalescence, to the same agents, led Huebner and his associates to change their designation from AD to APC viruses (adenoidal-pharyngeal-conjunctival).

During the summer of 1954, Bell and his associates[6] studied over three hundred cases occurring in three outbreaks of an acute respiratory illness which they called *pharyngoconjunctival fever*. This illness was similar to the small hospital outbreak just described, and adenovirus type 3 was isolated in HeLa cell culture tubes from the eye, throat, and anal swabs

Classical antibody rises confirmed the etiology. The clinical picture was characterized mainly by fever, sore throat, and conjunctivitis. In addition, there were headache and lassitude in the majority of cases. Fever, often the chief complaint, lasted for an average of five to six days (range, one to ten), and then came down by lysis. Sore throat was generally mild, being described more as "scratchy" rather than as painful swallowing. Physical findings were not striking except for injection of the posterior pharyngeal wall which was studded with glairy lymph follicles. Nontender, submaxillary lymph nodes were commonly felt. The conjunctivitis lasted for a few days to three weeks. Mild, follicular injection of both bulbar and palpebral conjunctivae was observed, often in one eye only. Exudate was rarely purulent. Scanty serous exudate with slight matting of eyelids and increased lacrimation were not uncommon. Photophobia and retro-orbital pain were practically nonexistent. No corneal or uveal involvement was seen. Otitis media was infrequent, usually nonpurulent, and did not seem to respond well to antibiotics. Muscle, bone, and joint aches, and weakness were seen occasionally, particularly in adults. Laboratory findings except for possible leukopenia were negative. There were no deaths.

While these studies were in progress, Ginsberg and his associates[7] in Cleveland took the cue from Hilleman that ARD and PAP in soldiers at Ft. Leonard Wood was caused by RI-67 virus (adenovirus type 4). They wondered if perhaps the ARD seen during World War II at Ft. Bragg and subsequently at other military installations might not have had a similar etiology. Human transmission experiments reported[8, 9] a decade earlier had indicated a probable viral etiology for PAP and ARD. Fortunately preinfection and convalescent sera had been saved from the donor and recipients of ARD material. It turned out that these individuals had developed neutralizing antibody to adenovirus type 4 but none to types 1, 2, or 3. Also in retrospect, it was found that the illness, ARD, had occurred in the majority of recipients who had no antibody in the preinoculation sera. Emergence and rise of type 4 antibodies occurred in all recipients whose preinoculation sera were devoid of antibodies. Moreover, the majority of recipients whose preinoculation sera contained type 4 antibodies had been resistant to experimental infection and did not show further increase in antibodies. It appeared likely from the evidence provided by these retrospective studies that adenovirus type 4 is related etiologically to ARD studied during World War II by the Commission for Acute Respiratory Diseases. Recently another member of the adenovirus group, known as type 7, has been isolated by Berge and his associates[10] from the throat washings in 44 per cent of respiratory illnesses studied at Fort Ord, California. Types 4 and 7 appear to be the two commonest adenoviruses associated with respiratory illness in military populations.

Population groups have been investigated[15] serologically for antibodies to the adenoviruses. Types 1 and 2 antibodies were found com-

monly in children. Type 3 antibodies were found in relation to outbreaks of nonbacterial pharyngitis. Antibodies to other types were infrequent in children. In Cleveland, type 4 antibodies have not been found in subjects under the age of 17 years. If this is found generally, it may partially explain why ARD infection with type 4 occurs in military recruits.[16]

Studies just begun in our laboratory[17] indicate a relationship between the adenoviruses and certain acute respiratory infections in infants admitted to Bellevue Hospital. Significant CF antibody rises were found in eleven of eighteen infants with bronchiolitis, two of eight infants with laryngotracheobronchitis, and none of five diagnosed as having bronchopneumonia.

Adenovirus type 8 has been described by Jawetz and his group.[11] These workers presented evidence for association of type 8 with epidemic keratoconjunctivitis (EKC). The agent was isolated from the eye of a seaman with typical EKC. Neutralizing antibody rises to this virus were reported in tests of paired sera from other patients.

Rowe[12] reported recently that the adenovirus family consists of at least seventeen serologically distinct viruses having similar properties, including common complement-fixing antigens. Three of these strains were isolated from primates and have not been associated with human illness.

Huebner and collaborators[13] have described the use of a killed type 3 vaccine in adult volunteers. Following injection of vaccine, antibodies were measured and the subjects were challenged with homologous virus. Significant protection was achieved and this was correlated with the presence of detectable antibody. These findings suggest that vaccines could be made with other members of this group, such as types 4 and 7, the predominating strains in ARD of military recruits. Hilleman[14] and others have recently reported the development of such a bivalent formalin-killed vaccine containing types 4 and 7. The vaccine was reported (1) to have stimulated high levels of neutralizing antibody and (2) to be at least 90 per cent effective in preventing acute respiratory illness of adenovirus etiology in recruits.

Today the interval between the isolation of new viruses and the preparation of effective vaccines appears to be shortening. The discovery of the adenoviruses represents a salient advance, but many problems in the field of respiratory infections remain to be conquered. Not the least of them is the common cold. So far, no relationship between the common cold and any members of the adenovirus group or any other known virus has been established.

REFERENCES

1. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G.: Isolation of a Cytopathogenic Agent From Human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **84**: 570, 1953.
2. Hilleman, M. R., and Werner, J. H.: Recovery of a New Agent From Patients With Acute Respiratory Illness, Proc. Soc. Exper. Biol. & Med. **85**: 183, 1954.
3. Rowe, W. P., Huebner, R. J., Hartley, J. W., Ward, T. G., and Parrot, R. H.: Studies on the Adenoidal-Pharyngeal-Conjunctival (APC) Group of Viruses, Am. J. Hyg. **61**: 197, 1955.
4. Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A.: Adenoidal-Pharyngeal-Conjunctival Agents,

A Newly Recognized Group of Common Respiratory System Viruses, New England J. Med. **251**: 1077, 1954.

5. Parrott, R. H., Rowe, W. P., Huebner, R. J., Bernton, H. W., and McCullogh, N. B.: Outbreak of Febrile Pharyngitis and Conjunctivitis Associated With Type 3 APC Virus Infection, New England J. Med. **251**: 1087, 1954.
6. Bell, J. A., Rowe, W. P., Engler, J. L., Parrott, R. H., and Huebner, R. J.: Pharyngoconjunctival Fever: Epidemiological Studies of a Recently Recognized Disease Entity, J. A. M. A. **157**: 1083, 1955.
7. Ginsberg, H. S., Badger, G. F., Dingle, J. H., Jordan, W. S., Jr., and Katz, S.: Etiologic Relationship of the RI-67 Agent to "Acute Respiratory Disease (ARD)," J. Clin. Invest. **34**: 820, 1955.
8. Commission on Acute Respiratory Diseases: The Transmission of Primary Atypical Pneumonia to Human Volunteers, Bull. Johns Hopkins Hosp. **79**: 97, 1946.
9. Commission on Acute Respiratory Diseases: Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter-passing Agents. II. Immunity on Reinoculation With Agents From the Two Types of Minor Respiratory Illness and From Primary Atypical Pneumonia, J. Clin. Invest. **26**: 974, 1947.
10. Berge, T. O., England, B., Mauris, C., Shuey, H. E., and Lennette, E. H.: Etiology of Acute Respiratory Disease Among Service Personnel at Fort Ord, California, Am. J. Hyg. **62**: 283, 1955.
11. Jawetz, E., Kimura, S., Nicholas, A. N., Thygeson, P., and Hanna, L.: New Type of APC Virus From Epidemic Keratoconjunctivitis, Science **122**: 1190, 1955.
12. Rowe, W. P.: Conference on Viruses in Search of Disease, New York Academy of Sciences, Section on Biology, May 24-25, 1956.
13. Huebner, R. J., Bell, J. A., Rowe, W. P., Ward, T. G., Suskind, R. G., Hartley, J. W., and Paffenbarger, R. S.: Studies of Adenoidal-Pharyngeal-Conjunctival Vaccines in Volunteers, J. A. M. A. **159**: 986, 1955.
14. Hilleman, M. R., Stallones, R. A., Gauld, R. L., Warfield, M. S., and Anderson, S. A.: Prevention of Acute Respiratory Illness in Recruits by Adenovirus (R I-APC-ARD) Vaccine, Proc. Soc. Exper. Biol. & Med. **92**: 377, 1956.
15. Jordan, W. S., Jr., Badger, G. F., Dingle, J. H., Ginsberg, H. S., and Katz, S.: Serologic Epidemiology of Respiratory Agents Isolated in HeLa Cell Cultures, J. Lab. & Clin. Med. **44**: 816, 1954.
16. Dingle, J. H., and Feller, A. E.: Non-influenzal Viral Infections of the Respiratory Tract, New England J. Med. **254**: 465, 1956.
17. Winter, J. L., and Chang, S.: Unpublished observations.
18. Enders, J. F., Bell, J. A., Dingle, J. H., Francis, T., Jr., Hilleman, M. R., Huebner, R. J., and Payne, A. M.-M.: "Adenoviruses": Group Name Proposed for New Respiratory Tract Viruses, Science **124**: 119, 1956.

Psychologic Aspects of Pediatrics

INFORMING THE PARENTS OF THE MENTALLY RETARDED CHILD

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

INFORMING the parents that their child is feeble-minded requires those qualities which are, by and large, prized most highly in the physician: firm knowledge of course, but equally important human understanding, sympathy for the parents without sentiment, concern for the child, insight, acceptance, the well-chosen word and phrase. This function of the physician remains paramount—it must not be obscured by the valuable, but still limited, techniques for treating the sick.

When parents consult the physician about their mentally retarded child, they want a clear-cut, unequivocal statement regarding the child's mental status. They want some discussion of the possible etiological factors. The child's future development is, of course, of prime concern to them. They will probably want to know about the possibility of subsequent children being similarly afflicted. What can they do to help the child? They may want advice about institutional care. Usually unspoken, but prominent in their minds, are reactions of guilt, resentment, rejection, shame, and inadequacy, and these need discussion. These are the points which I intend to cover.

The physician who is consulted about a slow child is actually asked to make two judgments: (1) is the child's behavior abnormally slow, and (2) is the retardation likely to be permanent? At one time it was assumed that once a slow child, always a slow child—and there are still too many who hold this view. But as we learn more and more about the irregularities in the developmental process, we become more and more cautious. Over the years one sees many children, at first slow in motor and speech development, later catch up and function normally, some even at a high level.

Obviously a prognosis as to the permanence or impermanence of the slowness is the more important judgment. In many instances, perhaps in most, the parents are already aware that the child is slow. But often they seem almost completely unaware of the possibility that the child may grow up to be weak-minded.

Before informing the parents that their child is mentally retarded and that he will never grow up to full adult mental power, the physician must be sure of his diagnosis. This is usually not too difficult but, in a

From the Department of Pediatrics, New York University College of Medicine, and Children's Medical Service, Bellevue Hospital.

Presented at an Institute on Mental Retardation and Associated Problems, Children's Hospital, Society of Los Angeles, April 9, 1956.

sizable proportion of cases, even the long-experienced physician will be uncertain.

PSEUDOFEEBLE-MINDEDNESS

A number of conditions which may confuse have been assembled under the general heading of pseudofeeble-mindedness. A severe visual defect may slow up development. Young children do not complain about poor vision, for the obvious reason that they have never known good vision. It is not always easy, in a young child, to tell whether retarded development is due to a visual defect or whether the mental defect came first. The same is true of an auditory defect.

Hydrocephalus may cause confusion. Many physicians regard all children with this condition as mentally retarded. This is by no means true. Hydrocephalus, if not too severe, is compatible with a high degree of mental functioning. Dr. Abraham Jacobi, the first professor of pediatries in America, had a very large head and he is quoted as having said that a little hydrocephalus stimulates mental functioning. Several years ago I saw a baby girl who was born with mild hydrocephalus and spina bifida. The father was given a bad prognosis as to the child's future mental progress. He told the mother, with the acquiescence of the physician, that the baby had died, and he had her transferred to Bellevue Hospital. The baby did nicely. The head, though large, did not grow inordinately. She was a pretty little girl and she soon became a ward favorite, thereby avoiding the rigors of hospitalism. The father was urged to inform his wife of the circumstances, to tell her that he had acted to save her from the anguish of having about her a deformed, idiot child, but he hesitated. The mother was finally told about the baby and came to see her at the hospital several times. The youngster is now 3 years old. She has a flaccid paralysis of the lower extremities and is in a rehabilitation unit. Her intelligence is in the low normal range. She has spent her whole life in hospitals. What a tragedy!

At the International Pediatric Congress in New York in 1947 Dr. Bronson Crothers presented a remarkable case, a child with normal-sized head and distinctly dilated ventricles who was functioning normally, despite the fact that the brain must have been reduced in size.

A not infrequent source of error is a delay in speech development. There is a sizable group of children, more commonly boys, who do not speak until they are 3 or 3½ years of age. These children may and usually do have entirely normal mental capacity, indeed they may have superior mental power, but they do not speak. The condition is often familial, there being other similar cases among near-relatives; and it is often associated with alterations in lateral dominance—ambidexterity, crossed dominance, e.g., right handedness and left eyedness, and so on—either in the child or in other members of the immediate family. When these children begin to speak, their verbalizations are at first difficult to understand, but they improve spontaneously over a period of several years and generally speak normally. Some retain speech defects like a lisp or a clutter.

In late talkers other possibilities must be considered—mental retardation, deafness, early infantile autism

—but a developmental abnormality is the most common cause. In general, a strong point in the differential diagnosis is the fact that motor development proceeds normally. But occasionally there are distortions here also and one must then rely on an estimate of the youngster's comprehension.

A severe neurological disorder, such as athetosis, may readily confuse with mental weakness, although these persons are usually normal mentally and, occasionally, even superior. The difficulties which the athetotics have in expressing themselves, owing to involvement of the muscles of articulation, are so extreme that one is likely to become impatient and not wait to hear them out.

A condition to keep in mind in assessing a child of school age is specific reading disability, by which is meant difficulty in recognizing the written word. This is a widespread defect, particularly in boys. Unfortunately it is often missed. This learning defect is compatible with a high degree of mental functioning. It is said that the great physician John Hunter was unable to read until he was 17 years old. Specific reading disability should be considered as a diagnostic possibility in every seemingly normal child who has difficulty at school.

There are probably other learning disabilities about which we know practically nothing at present.

It is said that every institute for mental defectives contains a certain number of schizophrenic children. In many instances the differential diagnosis between schizophrenia and mental retardation is extremely difficult. This is especially true of the early autistic children, whose symptoms are sometimes recognizable in the second year of life. If one is alerted to this condition, the mutism or word-distortions, in the presence of normal motor development, the indifference toward people, the anxiety which is expressed at even minor changes in the youngster's environment are generally sufficient to make a diagnosis. It is well to keep in mind the possibility of schizophrenia in the case of any suspect for mental deficiency whose physical appearance is normal and whose developmental history or behavior, or both, are bizarre.

The possibility of an adverse social and psychologic environment producing permanent damage to the mental functions has been widely debated in the psychiatric literature. There is little doubt but that a severely neglected infant or child will be slowed in his mental development; the controversy revolves around the question of the permanence of the damage. This discussion has recently been revived by Bourne, a New Zealand physician. In an article in the *Lancet* entitled "Protophrenia, a Study of Perverted Rearing and Mental Dwarfing," he described a group of children, reared in most unfavorable home circumstances, both economic and psychologic, who were severely retarded. It is his thesis that the unfavorable milieu was the cause of the mental dwarfing and that the damage is permanent. His presentation has been the basis for many letters to the *Lancet*. It has been suggested that these children were psychotic. Another suggestion was that, what with the limitation of institutional facilities, children were more likely to be taken for institutional care from bad homes than from

good ones; hence the preponderance of unfavorable homes among the children admitted.

Dr. Wayne Dennis, who has studied this problem intensively, concludes that neglect, even when severe, does not produce permanent damage to the mental faculties but that the children who are reported as being severely damaged by extreme neglect are neglected because they are, in the first place, defective.

Errors in mental testing may give a false impression of a child's mental power. Mental tests, like other laboratory tests, are subject to error. Some of these are "human errors." The child may make a bad impression on the tester by his behavior, his unusual appearance, a bad speech defect, and so on. The child may be excessively shy, tense, upset, suspicious, uncooperative, and so not perform up to his capabilities. There are some who would attribute the improved performance of young children on mental tests after attendance at a nursery school to release of this sort of mental blocking.

In assessing a child's mentality one should also keep in mind the possibility of the effect of depressing drugs as in the treatment of epilepsy.

Essential, then, when so serious a diagnosis and prognosis as mental retardation or feeble-mindedness are under consideration, is that the physician be sure of his ground. The diagnosis of feeble-mindedness rests on the medical history, the developmental history, the clinical examination, and psychologic tests.

HISTORY AND EXAMINATION

When a child is brought to the physician for evaluation of his mental status, a detailed history should be taken and a careful examination made. History should include full details of the family structure since this will help later on when it comes to advising about management. The wise physician will be sizing up the parents—their attitudes toward the child, toward one another, toward their other children—while he is assembling his data. The diagnosis may be evident at once, as in the case of many mongoloid children, but parents nowadays are not impressed, as they are said to have been at one time, by the physician who requires but a glance to arrive at a diagnosis. The parents should know that all necessary means have been used to establish a diagnosis. An ophthalmoscopic examination should always be included. Some time ago I saw a severely defective child with a history of anemia and severe jaundice during the newborn period requiring transfusion. The parents would have had me believe that the child had kernicterus. Eye-ground examination revealed the typical cherry red spot characteristic of amaurotic family idiocy. I learned later that the parents had already been told the correct diagnosis; they resisted accepting it and were looking for someone to tell them something else.

Eye-ground examination may reveal chorioretinitis, often associated with toxoplasmosis, or perhaps changes indicating an expanding lesion.

If there is any reason to believe that a pneumoencephalogram or electroencephalogram will help, remote though the possibility may be, such examinations should be made. The same holds true for other determinations such as protein-bound iodine,

roentgenograms of the bony centers, and so on.

Helpful in getting an office estimate of the child's mental status is the Draw-a-Person test introduced by Goodenough. A child's drawing of a person can be scored with results that correspond fairly closely to the more elaborate intelligence tests. The technique of testing is simple: the youngster is given a piece of paper and a pencil and asked to draw a person the best way he knows how. Most children like to draw and cooperation is usually readily obtained. Scoring is also simple. The test is most useful in ruling out feeble-mindedness in doubtful cases. One should not diagnose mental retardation in a doubtful case because the drawing is poor. I recently saw a 5½-year-old boy with an I. Q. score of 135 on the Stanford Binet test whose drawing of a person was a most primitive scrawl. The test sometimes is helpful in differentiating the child with schizophrenia who usually draws well, sometimes exceptionally so.

The purpose of the examination is by no means merely to impress the parent with the physician's seriousness and thoroughness, although this point is not to be minimized. It seems unfair to child and parents to undertake extensive studies if the diagnosis is readily apparent. But there are other reasons. The child may have a remediable condition like subdural hematoma or hypothyroidism. More often the importance of establishing a diagnosis is because of the question of heredity and the possibility that the condition may recur in subsequent children.

It is unwise to refer a child with a mental defect to a diagnostic clinic for work-up by a team. Above most other conditions, the family of a mentally retarded child needs the personalized approach which they can get only in the physician's office.

After a patient has been seen by a consultant, the family physician or the pediatrician should sit down with the family and interpret the consultant's report. Any vagueness or misinterpretation should be clarified. If necessary, the consultant should be contacted by the referring physician for further information. And one should never use a consultant whom one does not feel free to talk to in this way.

It is well to be cautious about predicting the future mental development of children with brain damage owing to severe anoxia at birth unless the damage is obviously severe. Such children sometimes brighten up, after a period of slow development, and function as normal individuals. Unless the damage is well marked, therefore, the parents may be given some hope.

INFORMING THE PARENTS

Before coming to the physician, the parents have often been informed that the child is retarded or they have themselves suspected it. Usually these cases are easy to handle and simply require confirmation. Much more difficult are those instances where the parents are unaware of their child's shortcomings or where they choose to conceal their knowledge—a not unusual situation.

The questions which the physician asks should be so phrased as to arouse suspicion in the minds of the parents: Does he grasp things as well as your other children when they were his age, or as well as your friends' children? Have you noticed that he plays differ-

ently from other children? Have you been impressed with his slowness in catching on to things? The mother will usually reply that the child is slower in general, and then may go on to tell how good is his memory for tunes or for faces or how wonderful is his sense of rhythm. The physician will do well to listen patiently to these words while the parents are bracing themselves for a verdict which they are now prepared to receive.

Once the physician has come to a firm decision that the child is feebleminded, he should state his opinion in frank, honest, and unequivocal terms. At the same time he should avoid offending the parents by using words which are distasteful, such as moron, imbecile, idiot, subnormal, defective, mongol, cretin. Instead he may say that the youngster is slow or retarded in development, but he should make it clear at once that the child will never catch up, that he will never be able to function as a normal grownup, that his brain will always remain like that of a child. No loophole must be left for misunderstanding since the parents, naturally, will seek, in any unclarities of the physician's statement, a straw at which to grasp.

It is important that the physician state his opinion clearly and in readily understandable terms. The use of obscure language confuses the parents and makes some suspect that the physician is trying to cover up his own ignorance in this way.

The parents will want to know whether the diagnosis is certain. When the diagnosis is straightforward and definite, as in the case of mongolism, the examiner should say so. But, where the least doubt exists, the physician may say something to the effect that miracles sometimes happen in medicine, that he would be very much surprised if the youngster would improve, but that he would be very happy to be wrong in his judgment about the future progress in this case.

If the physician is not sure of his opinion, he should so inform the parents. His uncertainty may be because medical science is incomplete; or it may be that his own knowledge and experience are limited. There is a positive way of telling parents one does not know. Whenever indicated one should seek help from consultants. The physician may say something to the effect: "I wish that I could give you a positive answer about your child's condition but I cannot at present. It is obvious that he is behind now, you realize that as well as I, that is why you brought him. But every once in a while one sees children, just like yours, catch up and develop quite normally. We shall simply have to wait before we make a final decision." Or "I want to have you see so-and-so who has made a special study of these children and has a large experience. When you have seen him, let us sit down together and discuss his report."

Whenever possible the physician should try to find favorable things to say about the child. A physician's comments about the attractiveness of the child, his nice manners, his sweet gentle disposition, perhaps a prediction as to his future development, modest though it will necessarily be, such as "he will be able to ride a bicycle," "she will be a lovable companion," help to lighten the blow.

Many parents find help from reading books and pamphlets of which there are several excellent ones. They

may be obtained from the National Association for Retarded Children, Box 85, Wall Street Station, New York City. Parents may be directed to the local council for retarded children. Most units maintain programs directed toward answering questions. At the same time they provide opportunities for parents with a similar problem to discuss their mutual concerns.

Let me say, at this point, that, much as I feel with the parents who would like a definite answer about their child's condition, such a definite answer cannot always be given, especially in the case of infants.

We would like to give parents the definite opinion they seek. But they must bear with patience the well-considered caution of the physician, whom ancient tradition and long experience have taught the frailty of human judgment.

Though most parents want to be told the truth about their youngster's condition, many certainly do not. A girl of 6, traumatized at birth, functioning at a low mental level and epileptic, was seen from time to time over a period of three years. At the outset the parents were given a glimmer of hope, because of the possibility that, with control of the convulsions and the passage of time, the child might improve. When the mental status failed to improve, the parents were told that the youngster had been observed over a period of years, that she was getting no better, that she would be permanently slow. The family has never been seen again. This is a common experience among physicians.

Many parents find solace in religion and are greatly helped in making an adjustment through this medium. It might be possible for the physician to collaborate with the religious counselor.

ETIOLOGY

In reply to questions regarding the cause of the defect we can only say that, with rare exceptions, it is unknown. Parents will often mention some distant relative who is afflicted with a mental disease, but this may be dismissed with the statement that mental disease is unfortunately so common that there is hardly a family without a victim. The physician should make a special effort to avoid having the parents blame themselves or one another for the child's difficulty.

FUTURE DEVELOPMENT

Of great concern to the parents is to what extent the child will develop. Will he learn to walk, talk, go to school, earn a living? A fair prediction can be made if the child is old enough to take a mental test. The idiot, whose mentality does not exceed 20 per cent of normal (I. Q. 20 or less), may learn to walk and say a few words, but nothing more. The imbecile, whose I. Q. range is between 20 and 40, will learn to walk and talk and take care of his personal needs, but he will not be able to go to school or earn a living. The intelligence range of the moron, who makes up the largest proportion of mental defectives, is fairly wide, from 40 to 70, and achievement varies in a general way with the intellectual capacity. The lower grade morons achieve little more than the imbeciles, but those with intelligence quotients between 60 and 70, the largest group, will be able to attend school, although they will either be below the proper grade for their age or be in an ungraded class. They are

often able to support themselves by manual labor or in certain occupations.

The intelligence quotient is a fairly good yardstick for predicting the rate of progress. Thus a child with an I. Q. of 50 at 5 years will function like a 4-year-old child at 8 years, a 5-year-old at 10 years, etc.

There are many individuals in the community with I. Q.'s in the range generally considered subnormal, that is, below 70, who function in the community as useful, self-supporting, self-directing members of society. Two studies in the literature illustrate this point, and both agree. The older study is that of Fairbank reported in 1933.

She gave a most illuminating report on the progress of 166 feeble-minded children, who had been found, in 1914, to have intelligence quotients between 61 and 72. It was prophesized at that time that these children were liable "to recruit the ranks of vagrancy, alcoholism, prostitution, delinquency and chronic dependence, reproducing without care and handing over to others their defective offspring." An altogether different picture was found, however, when 122 of these individuals, 50 girls and 72 boys, were reexamined seventeen years later. Only 4 had illegitimate children, 8 had a history of chronic alcoholism, 5 had court records after they reached adulthood, and 9 were being assisted by relief agencies before the depression. Ninety-five families out of 122 were financially independent, and 36 families owned or were buying their own homes. These men and women were employed principally as domestic workers and as unskilled laborers in factories, and clerks. Forty individuals were available for retesting, and in all instances the intelligence quotient had remained practically unchanged during the seventeen-year interval. Fifty of their children, all of school age, were given intelligence tests. Of these, 3 had I. Q.'s under 70, 4 had I. Q.'s over 120, and the rest had I. Q.'s between 90 and 110.

Similar findings regarding the socio-economic adjustment of morons were reported by Kennedy, who compared the kind of progress made by adult morons with that of a matched group of normal persons from a small urban community in Connecticut. Contrary to popular ideas, the morons did not make social menaces of themselves. They seldom committed serious offenses against other individuals or society in general. A few more of these men and women (20 per cent) got into trouble with the police, but their offenses were, for the most part, minor. The incidence of illegitimate children was somewhat higher but actually the frequency of illegitimacy was low. The marital records of the group did not differ materially from those of nonmorons. Divorces and desertions were somewhat more frequent.

The educational potentialities of the morons were poor, and only rarely did they progress beyond the grammar grades.

Most of them were self-supporting, and their earnings compared favorably with those of nonmorons. They were employed principally in unskilled work. On the whole, their work performance was not quite as satisfactory as that of nonmorons, according to employers' estimates.

Mrs. Kennedy concludes that morons are socially adequate in that they can be economically independent and self-

supporting and that they do not seriously threaten the safety of society.

In discussing the high-grade defective with the parents, therefore, we should remember that the moron can function as a normal member of society, doing jobs, contentedly, that the more intelligent members of society would find monotonous or distasteful but which are jobs, nevertheless, that must be done.

Parents may find consolation in the knowledge that the child himself will not be unhappy because of his handicap. Defective children, especially those below the grade of moron, appear unaware of their mental shortcomings.

MORE CHILDREN

Whether the parents ask about it or not, the advisability of having more children should be discussed. Except for certain congenital cerebral defects which are known to be familial, such as phenylpyruvic oligophrenia, they can be assured that the danger of mental deficiency is no greater for their subsequent children than for the children of any parents.

Amaurotic family idiocy is a special case. The parents should know that the probability of the same defect occurring in further children is high, approximately 25 per cent. Nevertheless in many instances siblings have been entirely normal, and it has therefore been our practice to advise parents to try a second pregnancy. It may help to point out that, should a second child be affected, the episode will be terminated before the child is 2 years old. If there have been two affected children in the family, the parents should be advised against trying again. The emotional trauma of going through a pregnancy with the imminent threat of again having an amaurotic child is more than most persons can endure. When the parents are unwilling to risk a second trial, artificial insemination may be suggested. Since the trait is recessive, it must be carried by both parents for the disease to be present.

Young parents who have had a mongolian child can safely be advised to have more children, since the incidence of a second mongol in the same family is low. In 2,491 families with mongols collected by Macklin mongolism occurred a second time in only 30 instances (about 1.2 per cent).

Penrose estimates that the chances of having a second mongol are about three times greater than in the general population. There is no point in telling this to the parents. They should be told, instead, that the chances of having a normal baby, that is, one who is not a mongol, are better than 99 out of 100.

The situation in older mothers is different. Here the incidence of mongolism in children born after the first mongol is relatively high, about 1 in 80 between ages 40 and 45, according to Penrose. In this age group, in 63 sibships in which 110 children were born after the first mongolian child, 16, or 14.5 per cent, were also mongols.

The gene for mongolism is widely distributed. Fortunately, penetrance is low.

PARENTAL REACTIONS TO THE FEEBLE-MINDED CHILD

The effect of having a feeble-minded child in the family is usually a profound one and differs in many respects from the situation where the child has a physical defect. A common early

reaction is unwillingness to accept the diagnosis. Consequently, there is a good deal of shopping around, with consequent confusion, as the meanings expressed by different physicians are discussed back and forth and often misinterpreted. A common parental reaction is guilt, generally because of imagined neglect or because of some minor, unrelated injury. When some antagonism already exists between the parents, the unfortunate child may be the focus around which recriminations and accusations revolve. On the other hand mutual misfortune may draw the parents closer together.

A common parental reaction to his own guilt feeling is oversolicitude and overprotection. We all know the mother who becomes a slave to her feeble-minded child. Resistance to institutional care is sometimes, but by no means always, partly on this basis of guilt feelings also.

Some parents regard the feeble-minded child as punishment for a past misdeed.

Rejection is also a common reaction and this is another reason why some parents have guilt feelings. The parent is repelled by the unfortunate child's mental inadequacies, by his grotesque physical appearance, by awareness of the social stigma which he has brought on the family.

On the other hand, many parents develop a very real affection for the feeble-minded youngster and center all their affection on him to the exclusion of other members of the family. It is important to remember that human emotions are usually mixed and that rejection and overaffection may and often do exist side by side.

Other parental attitudes are shame because of the social stigma of having a defective child, and feelings of inadequacy.

Knowing what the parental reactions are, the physician is in a good position to do something about them. Whether or not the matter is brought up, he should point out that the patients are in no way at fault, that science is entirely ignorant, at present, of why some children are born this way. The parents should be complimented on their patience and understanding, on the attention and affection which they have bestowed on the child. Favorable remarks from the physician on how well cared for the youngster is or on some aspect of his behavior or dress carry much weight with most parents and tend to diminish feelings of rejection.

INSTITUTIONAL CARE

The most vigorous criticisms of physicians by parents of retarded children center about the doctor's insistence on institutional care. It is true that institutional care offers certain advantages but the decision must remain with the parents. We should only suggest or recommend—we should under no circumstances insist. One should try to assess, from the general conversation, the parental attitude on this subject. If the parents are determined to keep the child at home, institutional care should not be mentioned. Ordinarily the subject may be brought up by asking whether the parents have thought about a special school for the youngster. If the answer is a vigorous no, the matter should be promptly dropped. If there is hesitation, one may suggest that the parents have the youngster registered for admission to

a state school. Since it will probably be a long time before there is an opening, they will have plenty of time to make a decision. In discussing institutional care the advantages to the child should be stressed rather than the advantages to the parents and siblings—he will not have to compete with children of normal mentality; he will be able to excel among children who are less advanced than he; he will be shielded from the jibes of his peers.

The institution is suitable for low-grade defectives who are unsightly, e.g., severe hydrocephalics; for the overactive, organic defective who is difficult to manage at home, although drugs are now available which are effective in controlling overactivity; for the moron who shows criminal tendencies; for some adolescent girls who are hard to supervise at home and are in danger of getting into sex difficulties; when having the defective child at home interferes too much with family life.

It helps greatly if the physician himself is acquainted with some of the institutes for mentally retarded children.

I see no reason why all severely defective children need be in an institution; actually the point is not whether I see it or not but what the parents feel. There are many high-minded people who regard it as their duty to accept their children as they are: "They are my flesh and blood; they are my responsibility and I will not shirk my responsibility." The social stigma is often the hardest of all to bear. Were it not for this, many parents who put their children in institutions would care for them at home happily. I believe that the reason why doctors, psychologists, and social workers urge institutional care is because they, too, feel that having a retarded child is shameful and that they want him hidden away in an institution. Is it not strange that, in a society like ours which regards itself as reasonable, an illness should be considered a family disgrace? There is need here for a campaign of enlightenment. An educational campaign to inform the public about mental retardation could do more good than many of the campaigns at present carried on for cancer check-ups, chest x-rays, and so on. At any rate such a campaign could do no harm by increasing anxiety as do many other campaigns. How successful it would be I do not know but I certainly think it worth trying.

Having a defective child in the home may be an ennobling influence for the family group. From the attitude and behavior of their parents toward the feeble-minded child, the other children will learn to be compassionate and helpful toward the less fortunate members of society.

Mongols.—Many pediatricians advise placing a newborn mongol immediately into an institution regardless of circumstances. It is my practice to tell the father the diagnosis at once. Unless he actively objects, I advise him to tell the mother, or to let me tell her. In general I advise institutional care, but I do not urge it, especially if the parents are older persons.

Mongols are, by and large, easy to take care of. They are docile, easy going, good natured, of sweet disposition, and rarely do the girls get into sex difficulties as adolescents and adults.

In certain instances the parents come to the doctor wanting to be told to place the child in an institution. I recently encountered such a case. This was a young couple, both intelligent and sensible, whose first and only 3-year-old child was defective. The diagnosis was not straightforward. The neurologist who had seen the youngster—one of the best children's neurologists in the country—could not decide whether the child had been injured at birth or whether he had early infantile autism. There was good reason to suspect autism; the child had none of the stigmas which one expects in a severely retarded young child—the small head, blank facial expression, and so on. His appearance was quite normal and he showed considerable interest in things, none whatsoever in people. His developmental history was also irregular and he showed flashes of unexpected intelligence. The consultant's doubts had been transferred to the parents, but of one thing these intelligent parents were sure: the child was functioning at a very low mental level. They felt frustrated by the doubts of their doctors. They wanted to go ahead and build a family. They wanted to feel that they had done everything possible for this child and they came really asking to be told this. When they were told that, regardless of the diagnosis, their child was severely defective, that there was not a chance in a million that he would develop socially acceptable behavior, that the proper thing for all concerned was to place him in a school where he would be well looked after, that there was no reason to believe that subsequent children would be similarly afflicted, that they would be wise to go ahead and build a family, I believe they were greatly relieved.

Doctors sometimes become intrigued by the diagnostic possibilities in a particular case and forget that the parents are not interested in refinements of differentiation but simply want to know about the child's mental status and his future potentialities.

MANAGEMENT

A question almost always asked by the parents when they are informed that their child is feeble-minded is: "What can we do for him?" This is a difficult question to answer since there is so little that one can do. It is wise, in most instances, to start by saying they have done a splendid job this far. A retarded child needs affection and praise and acceptance just like any other child, and these things they have obviously given him. But the youngster must learn to conform and to obey like other children. He should be expected to care for his needs within the limits of his mental capacity. A feeble-minded child, like a normal one, can be spoiled by too much affection as well as by too little. The child with an I. Q. of 50 or over can be taught habits of cleanliness, neatness, and courtesy. He should learn to listen and not to interrupt. A good listener is always appreciated. Efforts should be made to correct visual, auditory, or speech defects if they are present. Siblings should be taught to be helpful and understanding and not to tease.

Book learning will not help these children but those with I. Q.'s above 50 usually can be taught to read simple directions and to understand money.

The parents should always be invited to return at a specified time. They should be made to feel that the physician has a continued interest in their child.

SUMMARY

1. The parents should be told frankly and openly, yet kindly, about the mental condition of their child.

2. Certain offensive words like idiot, moron, cretin, mongol, and so on, should be avoided.

3. A few complimentary words about the child help to lighten the blow.

4. Discussion should be designed to allay guilt and rejection feelings.

5. Topics which parents want discussed are etiology, heredity, subsequent children, future development of the patient.

6. The subject of institutional care should be approached carefully.

7. The parents should be assured of the continued interest of the physician.

REFERENCES

Bourne, H.: Protophrenia, A Study of Perverted Rearing and Mental Retardation, Lancet **2:** 1156, 1955.

Brennemann, J.: Approach to the Parents of a Subnormal Child, in Brennemann's Practice of Pediatrics, Hagerstown, Md., 1945, W. F. Prior Co., vol. 4, chap. 13, p. 53.

Dennis, W.: Significance of Feral Man, Am. J. Psychol. **54:** 425, 1941.

Doll, E. A.: Counseling Parents of Severely Retarded Children, J. Clin. Psychol. 9: 114, 1953.

Jensen, R. A.: The Clinical Management of the Mentally Retarded Child and the Parents, Am. J. Psychiat. **106:** 830, 1950.

Kanner, L.: Parents' Feelings About Retarded Children, Am. J. Ment. Deficiency **57:** 375, 1953.

Zwerling, I.: Initial Counseling of Parents With Mentally Retarded Children, J. PEDIAT. **44:** 469, 1954.

Pediatric Profiles

Heinrich Finkelstein

(1865-1942)

IN 1906, when I was a young assistant in a university hospital, it was my good fortune to review some of Finkelstein's recent work in the Infant Asylum in Berlin. This so impressed me that I took a few days off, made a trip to Berlin, and applied for an assistantship in the Infant Asylum. I was accepted and became Finkelstein's assistant from 1907 to 1914. During this time and for many years later Finkelstein was my teacher and adviser, and I was in close contact with him until his death. This may enable me to give a brief account of his life and work.

Heinrich Finkelstein was born on July 31, 1865, in Leipzig, Germany. In 1884 he began to study natural sciences. During the years of 1884 to 1886 he wrote a diary which is in my possession. It discloses the nature and character of young Finkelstein; page after page gives proof of his high ideals, of his love for nature and for mountains. Enthusiastic poems are devoted to their beauty. Another prominent feature disclosed in the diary is his shyness, which was apparently very disturbing to him. An entry in his diary, made at 2 A.M. one morning, is characteristic: "I just returned from a party. Little amusement. I behaved again very stupidly. My shyness is interpreted as lack of good behavior, while it arises from reserve only. It is necessary to eradicate this defect of mine, and to overcome the shyness." Finkelstein never succeeded completely in this respect. From 1885 on, he turned more and more to geology. In 1888 he received his Doctor of Philosophy degree. He had graduated with high honors. Four notable papers concerning the geology of the Alps had been published by him; however, the economic situation

of his family forced him to turn to medicine, which promised a better income in a shorter time, and, with that, the possibility of helping his family financially.

The study of the great problems of the history of earth and mankind may have influenced his pediatric work. What attracted him was not the casuistic, but the great problems in pediatrics. "When one has as his goal a small hill, one should not be surprised that one is not on the peak of the Jungfrau." Finkelstein received his medical degree in 1892 at the age of 37 years. From then until 1894, he was assistant in a hospital in Berlin. Attracted by the fascinating lectures of Heubner, he became his assistant at the University Children's Hospital of the Berlin Charité, where he remained for seven years. He became professor in 1899, and was appointed head of the Infant Asylum and City Orphanage of Berlin in 1901. In 1918, he became director of the Kaiser and Kaiserin Friedrich Children's Hospital of Berlin, where he stayed until 1933. The last years of his life were darkened by the political events in Germany. He was forced to leave his country, and emigrated to Chile following an invitation from his generous friend, Professor Seroggie. Here "he found a peaceful harbor from immense tragedy" (Dr. P. Pascual), greatly honored by the South American physicians. He died on January 28, 1942, in Santiago.

Finkelstein's work at the Charité was devoted chiefly to the problem of hospitalism. At this time the mortality from diarrhea was so high in infant wards that Henoch, the predecessor of Heubner, had suggested to Heubner that the infant ward of the Charité be abolished. By means of well-studied plans of isolation, aseptic nursery, and proper feeding Finkelstein was able to reduce the high death rate materially.

When Finkelstein became chief of the Infant Asylum in 1901, the infant mortality there was still 50 per cent. In two years it decreased to 10 per cent. The factors responsible for this great progress were not only aseptic nursery technique, but predominantly infant feeding on a scientific basis, and with this we enter the field of Finkelstein's most creative work: nutrition and nutritional disorders in infants. His investigations opened new horizons in pediatrics, and were the basis of his world-wide reputation.

It is not possible to enumerate all the important results of his research, but a few may be mentioned here.

1. Finkelstein and Czerny were the originators of the concept that diarrheal disorders in infants are not only local intestinal conditions, but predominantly parenteral metabolic disturbances.

2. Finkelstein studied systematically the effect of the individual food components and their correlation with the intestinal and parenteral processes.

3. The disorders of water, salt, and sugar metabolism were investigated extensively, and parenteral fluid therapy was early recommended for dehydrated infants.

4. The role of nutrition and mineral metabolism in the etiology of spasmophilia was studied and clarified.

5. Finkelstein introduced the much-discussed concept of alimentary fever.

6. He made important contributions to the problem of constitutional hydrolability.

7. With L. F. Meyer, he originated protein milk which appeared, at that

time, of such importance that Brennemann spoke of "a new era in pediatrics which could only be appreciated by physicians who had practiced prior to its introduction." For many years protein milk was standard treatment for severe diarrhea.

8. Intensive studies were devoted to many other problems, including eczema, pachymeningitis (subdural hematoma), and pylorospasm.

These investigations benefited children all over the world. The pediatric literature is impregnated with Finkelstein's ideas, but only those who have witnessed his work in the Infant Asylum personally appreciate his creative ideas, and the devotion and enthusiasm which he carried to each new problem. Frequently his fantasy was far ahead, but his self-criticism did not allow premature conclusions. Results had to be re-examined again and again until the evidence was conclusive, but how much happiness was then in the Infant Asylum, irradiating from the Chief to all his collaborators. And they came from all over the world to receive instruction and inspiration from the great teacher.

Finkelstein was first of all a *clinician*. His teacher, Otto Heubner, made the following remark about his work: "It is perhaps not accidental that the basis of Finkelstein's important work is clinical observation and clinical experimentation, and not so much laboratory work." Everybody who has made rounds with Finkelstein can testify to that. His keen observation, combined with clear thinking, enabled him to discover and describe many features of the sick child which were significant for diagnosis as well as for treatment. Of course, he had great respect for the laboratory, but he refused to use each new laboratory method for systematic investigation just because it was new. Finkelstein was at home in pathological anatomy. At the Infant Asylum we assistants had to do the autopsies ourselves. I remember many a case of congenital malformation of the heart which we, with shaking hands, vainly tried to dissect. It always ended in the same way. Finkelstein took knife and scissors and demonstrated his superior technique.

Finkelstein was a *good teacher*. He gave us, with every round, examples of sound clinical observation. He forced us to be critical and to prevent logical errors in our conclusions. He developed our sense of responsibility so strongly that in all the years of my practice the silent question of my teacher has accompanied me: "Did you give the right treatment?" He taught us to be reserved and critical in our own publications. He read our papers very thoroughly, and kept them sometimes for months in his desk because he considered them premature. Yes, some papers have never seen the daylight again, but I feel that this system has prevented quite a number of premature failures. Finkelstein was an *inspiring teacher*. He was always full of ideas and problems. As if a tree is shaken, the fruits fell down as yet unripened. But many a fruit has ripened later, and sometimes somewhere else in the world. Dr. Isaac Abt described Finkelstein's lectures as follows: "When I attended his lectures, I was immediately impressed by his scholarship. He was not a facile lecturer; indeed, he was ill at ease in front of an audience and spoke hesitantly, though he had an amazing command of many languages. But his examinations and the interpretation of his findings were unsurpassed, and

made him an outstanding example of the old-time clinical investigator."

Finkelstein's *literary work* includes about 200 original papers, dealing with a wide variety of subjects. He was co-editor of the *Zeitschrift und Zentralblatt für Kinderheilkunde*, of the *Handbook of Children's Diseases* by Pfaundler and Schlossmann, of Feer's *Textbook for Children's Diseases*, and the beautiful *Atlas of Skin Diseases and Syphilis in Children*. His outstanding contribution was his *Textbook on Diseases of Infancy*. This textbook is a complete and masterful presentation of the whole subject based on his fundamental scientific work, his great practical experience, his extensive knowledge of the literature, and strong criticism. It is unique in the world literature. Other features of the book characteristic of Finkelstein's personality are mentioned in Pfaundler's review: "It is amazing how few 'I's' one finds in this book, even there where everybody would expect it." The same modesty is illustrated in Finkelstein's epilogue on artificial feeding: "There seems to be no reason to be jubilant about the great advances we have made. We have made less real progress than eliminated false ideas and learned to avoid mistakes." Finkelstein's *Textbook* went through four German and three Spanish editions. The last German edition was printed and published in 1938 in Holland. There was no sale in Germany during the Hitler regime. Finkelstein has expressed to me repeatedly his disappointment that there was no interest in having his book translated in English. A great success was the *Atlas of Skin Diseases and Syphilis in Children*, published with Galewski and Halberstaedter. At the time of the preparation of this atlas we were eager to collect cases that could be incorporated. One day a baby was admitted with a peculiar crusty rash on the soles of both feet. A dermatologist made a diagnosis of a rare disease, described only twice before in the literature. The next morning a moulage was to be made and the artist appeared. There was no longer any rash! The nurse had scrubbed the baby thoroughly; the "rash" had been an accumulation of dirt. On this day the Chief was in a very bad mood.

Finkelstein was a *quiet speaker*. His sentences were clear and in perfect form. He was not brilliant, but he impressed one by the content of his discussions. Confronted with the insulting remarks of a robust speaker, he was helpless. He could not strike back. Polemic attitude and offending criticism were not part of his character.

In his *private life* Finkelstein was very modest. He remained single and lived together with his sister, a well-educated lady with a great interest in literature. He did not attend splendid parties. His meals were modest. In the Infant Asylum his lunch consisted of milk and dry bread. He hated pose and pathos. He was shy and sensitive, but this sensitivity was less of constitutional origin than due to disappointments in his life. He concealed his shyness frequently behind the mask of fine irony. He did not develop a lucrative practice; in fact, he gave the majority of his clientele to his aides. His interest in material prosperity was slight. What made him happiest was intellectual work. He was fanatic in pursuing his problems and he was indefatigable in giving the finishing touch to his writing, but then the style was crystal clear and elegant. I

lived in his neighborhood for years. Whenever I came home at late hours his desk lamp was still burning.

Finkelstein had an unusual knowledge of many branches of science and literature. He spoke German, French, English, and Italian. When he went to Chile he acquired considerable facility with Spanish. Being a German Professor and Geheimrat, he had some of this professorial attitude in earlier years. He was reserved and kept a certain distance from his assistants. However, a remarkable change in his attitude took place after his first American trip. The Professor and Geheimrat disappeared, and only the doctor remained.

Finkelstein had one great hobby, *mountain climbing*. His love for the mountains was early awakened by his father, who also was an ardent mountaineer. Every year Finkelstein spent his vacation in Switzerland or the Dolomites, and he accomplished difficult ascents of the peaks, including Matterhorn, Monte Rosa, Mont Blanc, and others. On more than 600 high peaks and in innumerable valleys he could see the wonders of the mountains, and many of his ascents required great courage and alpine skill. In wintertime he did some physical exercise to keep fit for the mountains. In his simple bedroom you could see a ladder, ropes, and other equipment for training. One of the most dangerous tours has been described by him in the *Alpenvereinsblättern*, an ascent of Mt. Blanc in which his group was surprised by heavy snowstorms and had to spend the night in a small hut close to Mt. Blanc. He writes: "Never before has the word of the cruelty of Nature become so clear to me as in that long, stormy night upon the Cabane des bosses." Fortunately, the next morning the storm decreased and the group could descend to Chamonix. But this adventure did not prevent him from making dangerous alpine ascents year by year afterward. Finkelstein's love for the mountains lasted until the end of his life. Shortly before he had to leave Germany he went once more with rucksack and hammer to his beloved Aschau in Bavaria where, decades before, his geological thesis originated. When he was beyond 70 he buckled on the skis for the snow-covered Andes. His advice to the youth was to "go out into the mountains, not for adventure or for record, but to enjoy the beauty and grandeur of the mountains, where and in whatever form they present themselves: on the peaks or in the valleys; in rock, ice, water and clouds; in plant and animal; in human being and human work."

Finkelstein's ties to the United States and South America were very strong. His closest American friend was Isaac A. Abt. Abt brought Finkelstein to this country on a lecture tour, and "he took care of him like a brother." The devotion of the South American physicians brightened the last years of Finkelstein's life.

The younger generation does not know much about Finkelstein. They have their own heroes, and progress is so rapid that there is no time for them to stop and look backward. We of the older generation are conscious of the great contributions of our teachers, which have made possible the progress of today.

I. Rosenstern.

Comments on Current Literature

BENIGN MYALGIC ENCEPHALOMYELITIS (AKUREYRI DISEASE, ICELAND DISEASE)

DURING the winter of 1948–1949, an epidemic involving 465 cases occurred in Akureyri, in northern Iceland, a town of 6,900 population at that time. This disease seemed to be a distinct clinical entity with manifestations simulating in many respects those of poliomyelitis. The highest attack rate was in the age group from 15 to 19 years, but the incidence was high also among young adults generally. Very few cases occurred in children under 5 years of age. Sigurdsson and his associates,[1, 2] who studied this epidemic at the time and conducted a follow-up survey six years later (June, 1955), have summarized the main features of the disease: incubation period about one week, with onset of symptoms insidious, as a rule, but quite sudden in some instances; low-grade fever with headache, often in the back of the head; pains in the back and shoulders, radiating into one or more limbs; and painful muscles, usually tender to the touch. The patients complained of fatigue, following even slight exertion, of excessive nervousness, and sleeplessness, and some experienced loss of memory. Emotional disturbances were common. Paresis of muscles became apparent from two days to four weeks after onset of illness with a tendency in some patients to relapse, and the occurrence of paresis in other muscles, previously uninvolved. These relapses occurred as late as eight weeks after the initial paresis was observed. In some instances this muscle paresis was limited to one muscle or to a group of muscles, to one limb; or more than one limb might be involved. In all except the most severe cases, tendon reflexes were present, but decreased.

While in general the paresis tended to improve in time, the course was almost invariably a prolonged one, and disturbances in sensation, including numbness, paresthesia, hypesthesia, and hypalgesia, were relatively common. Emotional disturbances and instability tended to persist for long periods, during the prolonged convalescence, and easy fatigability persisted for weeks, months, or even years in some instances. During the acute stage, true nuchal rigidity was seldom observed, but patients did complain of pain in the neck region and down the back when the head was bent forward. No true back rigidity, in the sense of the "poker-like back" characteristic of early poliomyelitis, was observed. In most cases the spinal fluid findings, including the cell count, were within normal range. In the epidemic in Akureyri the incidence of clinical infection was high, 465 cases in a population of 6,900 (6.7 per cent), and although paresis was marked in 129 of these 465 cases, there were no deaths.

The careful study and tabulation of the manifestations of this disease in Iceland,[1] which simulated poliomyelitis in some respects but which did not fit in with the clinical picture of poliomyelitis, aroused considerable interest in medical circles, and since 1950 a number of reports has appeared describing similar outbreaks in which the clinical condition observed was difficult to classify and was referred to simply as "not po-

liomyelitis.'' Such outbreaks have been reported in New York State, London, Coventry, Berlin, in Adelaide, Australia, and in South Africa. In none of these outbreaks could any virus be isolated, nor has there been any laboratory evidence of infection with a known viral agent.

In the May 26, 1956, issue of *Lancet* several articles appear which throw additional light on this interesting clinical entity. Sigurdsson and Gudmundsson[2] of the Iceland group of investigators report the residual findings in some of the patients six years after the outbreak in Akureyri. They were able to study in detail thirty-nine patients who had been observed carefully at the time of the original outbreak in 1948–1949. Of these thirty-nine patients, who were subjected to complete neurological reexamination, all except one had engaged in his (or her) normal activity in the interim. The one who was not working was suffering from a gastric ulcer at this time. Of the thirty-nine, only twelve, or 31 per cent, were free from objective clinical manifestations, and only five considered themselves completely recovered. Thirty-two had nervous or neurological complaints, including twenty with muscle tenderness, and eighteen with demonstrable neurological signs. Nervousness and easy fatigability were reported by twenty-eight of the patients, muscle pain by twenty-four; paresis was apparent in nine, atrophy of the muscles in six, and reflex abnormalities were observed in six. Two patients complained of tenderness over nerves, and eight were still experiencing hypalgesia, hypesthesia, or dysesthesia. Although the disturbances of cutaneous sensibility were slight, their distribution was definite, either following the nerves or corresponding to the spinal segments. This interesting follow-up report serves to emphasize that although the clinical entity occurring in Iceland was not associated with fatal outcome, a significant number of patients did have troublesome sequelae some years after the initial illness. The authors felt that any possibility of hysteria in these patients was minimized by confirmatory demonstration of objective neurologic findings.

In the same issue of *Lancet,* Sumner[3] describes a small ''explosive outbreak'' of a disease resembling poliomyelitis. Seven young British soldiers were involved, six of whom lived in the same barracks block in Berlin. The seventh case was that of the orderly who nursed the other patients. The outbreak, which occurred in November, was considered explosive in character, since the last victim became ill only eight days after the first. Characteristic of this illness were extreme muscle tenderness, with neither paralysis nor reflex changes, and with normal cerebrospinal fluid, and mild but persistent mental changes. There was a tendency for these patients to have hyperacusis, conjunctival injection, and nystagmus. Recrudescence of symptoms after several days was common. In all seven instances, the course of the illness was prolonged; recovery was slow, with a tendency to depression in some of the patients. Efforts to establish the etiology by animal inoculation, tissue culture methods, and antibody studies were without success.

A third article appearing in this issue of *Lancet* is by Ramsay and O'Sullivan,[4] entitled ''Encephalomyelitis Simulating Poliomyelitis,'' and concerns the sporadic occurrence of a similar clinical entity (eight cases) in northwest London in the summer and autumn of 1955. Early symptoms in all eight cases consisted of lassitude and inertia, anorexia, nausea, and vomiting, followed by muscular pains and cramps, muscle twitching, giddiness, and transient or persistent tinnitus. Other manifestations included various degrees of neck stiffness with pain on flexion, exaggerated reflexes, muscle tenderness, which was marked in some cases, paresis, and in four of the eight patients signs of cranial nerve involvement. In seven of the

cases, lymphadenopathy was a characteristic feature, the posterior cervical lymph nodes being those chiefly involved. The blood picture in all eight cases was described as "characteristic of a virus infection—i.e., neutropenia with inconstant abnormal lymphocytes."[4] These abnormal lymphocytes observed in the blood smears were not considered sufficiently characteristic to be of diagnostic significance. In all cases the cerebrospinal fluid findings were within normal limits. Despite intensive laboratory investigations by animal inoculation, tissue culture methods and serologic studies for antibody development, no etiological diagnosis could be made.

Again, recovery was slow, convalescence was protracted, with residual mental and physical fatigue, and marked emotional instability in about one-half the cases. Three of the eight patients showed persistent weakness and sensory impairment four to six months after onset, and some degree of residual disability occurred in five of the eight. Electromyographic studies, which were carried out on all eight patients, are of interest; "the weakened muscles showed abnormalities of motor-unit activity revealed by the electromyographic pattern, but in no instance was evidence of lower-motor-neurone degeneration detected."[4] The changes were interpreted as typical of early myelopathic lesions, but as giving no evidence of lower motor-neuron degeneration. "In some instances where muscle weakness was severe all the residual motor units were abnormal and grouped, the volitional pattern being distinctive."[4] Electroencephalograms were obtained in the case of five of the patients who showed serious disorders of behavior. The tracings in all five were similar, showing abnormal rhythm; these electroencephalographic changes, however, were interpreted as nonspecific.

In an excellent editorial carried by the same issue of *Lancet*,[5] attention is drawn to this "new clinical entity." After a careful evaluation of the information available, the following editorial commentary appears: "It remains to identify this syndrome more precisely; but we believe that its characteristics are now sufficiently clear to differentiate it from poliomyelitis, epidemic myalgia, glandular fever, the forms of epidemic encephalitis already described, and, need it be said, hysteria.."[5] The editors stress the value of electromyographic records such as those obtained by Ramsay and O'Sullivan, which provide evidence of organic paresis in patients suffering from this clinical syndrome which has been designated as "not poliomyelitis." The term suggested by the editors of *Lancet*, "benign myalgic encephalomyelitis," seems an acceptable designation until further studies establish the etiology of this disease entity.

RUSSELL J. BLATTNER

REFERENCES

1. Sigurdsson, Björn, Sigurjónsson, Július, Sigurdsson, Jón H. J., Thorkelsson, Jóhann, and Gudmundsson, K. R.: A Disease Epidemic in Iceland Simulating Poliomyelitis, Am. J. Hyg. **52**: 222, 1950.
2. Sigurdsson, Björn, and Gudmundsson, K. R.: Clinical Findings Six Years After Outbreak of Akureyri Disease, Lancet **1**: 766, 1956.
3. Sumner, D. W.: Further Outbreak of a Disease Resembling Poliomyelitis, Lancet **1**: 764, 1956.
4. Ramsay, A. M., and O'Sullivan, E.: Encephalomyelitis Simulating Poliomyelitis, Lancet **1**: 761, 1956.
5. Editorial: A New Clinical Entity? Lancet **1**: 789, 1956.

Correspondence

A LETTER FROM LONDON

In England, as no doubt in the U. S. A., the mortality rates for children suffering from infectious diseases have decreased in a way that is really startling. For example, the death rate per 100,000 for children 5 to 9 years of age was for infectious diseases (including tuberculosis) 22.7 in 1946, whereas in 1952 the figure was only 6.5. For children 10 to 14 years the fall was from 19.6 to 4.9. Diphtheria is, of course, a rare disease with us now, just as is the case in the U. S. A. The rates for other causes have fallen to about two-thirds of their 1946 value, and we can regard the general health of our school children as very satisfactory.

When it comes to dental caries the picture is not so good; in fact, for 1953, the figures from all areas showed a substantial increase in caries above the 1948 figures. The Child Dental Health Committee of the British Dental Association regard as the most likely cause of this the almost incessant consumption of sweets, chocolate, and buns that has become habitual to the children of far too many ignorant and overindulgent parents.

There is no doubt that the rise in the standard of living carries in its train certain disadvantages. For example, the less well-educated parents, most of whom are so much better off now, indulge their children not only by giving many more sweets between meals than in years gone by, but by lavishing on them expensive toys in such a way that they have difficulty in learning any sense of values.

We have now in this country embarked on a pilot scheme of inoculation of children against poliomyelitis; the vaccine has been prepared by two commercial firms under the auspices of the Medical Research Council and the Ministry of Health. The British vaccine contains strains of the following three types of virus: Type I, an attenuated variant of the Brunhilde strain (not the Mahoney strain which was used in the U. S. vaccine), Type II, Middle East Force I strain, and Type III of the Saukett strain. The first phase of the antipoliomyelitis vaccination program is due to end June 30 and will now be confined to 200,000 children in Great Britain; safety tests cannot be completed in time to enable Local Authorities to arrange for the inoculation of more children by that date. However, a much greater number of children will undoubtedly be protected in this way in the near future, and the plans for this are fully prepared.

Early in 1954, plans were announced for a liaison between the Hospital for Sick Children, Great Ormond Street in London, and the Uganda Medical Service and Makerere College Medical Faculty. This liaison is now complete; two nursing sisters from the hospital in London have taken charge of the children's ward in the Hospital in Kampala, and a "senior registrar" (a medical man of similar standing to one of your senior resident grade) has been seconded from the Hospital for Sick Children, for a period of two years, in order to take part in the work and teaching of the pediatric department at Mulago Hospital in Kampala. This is the teaching hospital for the medical school of Makerere College, and is reserved entirely for African patients; it is an integral part of the Uganda Medical Service, and Makerere College and its medical school are maintained by the territories of Uganda, Kenya, and Tanganyika. Each year, according to the arrangements made, a member of the consulting staff of The Children's Hospital, in Great Ormond Street, will spend some weeks in Uganda, and will presumably take part in and advise on the pediatric work there.

What may be termed tropical pediatrics is a young subject, but a great stimulus to its pursuit has no doubt been given by the work on kwashiorkor carried out at Mulago. The association between a London teaching

hospital, the East African University, and the Uganda Medical Service is to be warmly welcomed, for it is likely to have a far-reaching influence.

In April, 1955, our Government's decision to ban the manufacture and export of heroin, except in small quantities for scientific purposes, was announced. This decision has been taken in order to give effect to a resolution adopted by the United Nations Economic and Social Council. Such a resolution resulted, of course, from a desire to counter drug addiction.

It soon became apparent that there was very considerable opposition to this from a large and influential section of the medical profession. It was pointed out that there was really no efficient substitute for this drug in relieving pain in certain diseases, and that the ban would have little effect in relation to addiction to this drug, because it could easily be manufactured in a back room by anyone determined to do so. Furthermore, interference with the right of a medical man to prescribe any drug he might think proper for a given patient was considered, on principle, to be a grave mistake. After a great deal of agitation the prohibition order was dropped because of a technical legal point which hampered Government action. One was left with the impression that members of the Government were probably rather relieved that a convenient loophole, saving them from some embarrassment, had presented itself at the last moment.

With the prospect of the International Congress in Paediatrics about to open in Copenhagen next month, many of us are looking forward to meeting friends from the United States who will be coming to Europe to attend it. We hope there will be many such visitors, and that not a few of them will spare at least a little time to visit us in England during their trip. A joint dinner has been arranged for members of the British Paediatric Association and the Academy of Pediatrics to be held on July 18 at the Mansion House, which is the official residence of the Lord Mayor of London. The Lord Mayor himself is attending as a guest, accompanied by two of his Sheriffs.

KENNETH H. TALLERMAN.

To the Editor:

We have read with interest the exchange of letter and editorial comment on acute barbiturate poisoning in the June, 1956, issue of THE JOURNAL OF PEDIATRICS. The conflicting literature on analeptics, and the death of the patient in spite of their use, underlines the need for a more direct approach to the general problem of exogenous toxins. In absence of a specific chemical antidote, the therapeutic goal should be removal of the poison from the body. In the case of barbiturates, this can be accomplished quickly and safely by hemodialysis. Experiences with a Kolff-Merrill artificial kidney in the treatment of acute barbiturate poisoning in adults are described in an article from this laboratory to be published in the *J. A. M. A.* within the next two months. The data presented on drug removal, lowering of blood levels, and clinical results in severely poisoned patients offer, we believe, conclusive evidence that hemodialysis is the method of choice in patients whose ingested dose of barbiturate and/or blood level is in the potentially fatal range for the particular drug in question.

The hemodialysis of young children is completely safe in experienced hands. The efficiency of drug removal, in comparison with that of adults, may be considerably greater because of the relatively small body depots in the former. It is, therefore, not entirely justified to assume that "irreversible depression and damage of the central nervous system" were present in the particular case described, in view of the child's continuous exposure to high blood levels of barbiturate up to the moment of death.

The availability of the artificial kidney depends, of course, on the patient's location. Greensboro, North Carolina, is, however, less than two hours by air from any of three properly equipped centers.

The above remarks apply with equal justification to poisonings with salicylate, bromide, and thiocyanate. The list is a progressively lengthening one, and unpublished data, not referred to in this communication, have already added to it.

LEONARD B. BERMAN, M.D.,
Georgetown University Hospital,
Washington, D. C.

DR. ETTELDORF replied as follows:

Dr. Woodbury and myself read with interest the letter that Dr. Leonard B. Berman

wrote concerning our editorial comment on barbiturate poisoning which appeared in the June, 1956, issue of THE JOURNAL OF PEDIATRICS. We would like to restate that no single therapeutic measure including hemodialysis should be relied upon to the exclusion of other measures. In this respect general support of circulation and respiration must be re-emphasized.

Our comment concerning irreversible changes that occurred in the particular patient which was discussed by Dr. John Wilson was referable to the effects of prolonged hypoxia and inadequate circulation and was not intended to mean that it was our opinion that the barbiturate concentration per se caused irreversible damage to the vital centers.

News and Notes

Dr. Jean Valjean Cooke, Professor Emeritus of Pediatrics at the Washington University School of Medicine, died in St. Louis, June 29, 1956, after a long illness. He had passed his seventy-third birthday only ten days before his death. He was a graduate of Yale and received his M.D. degree from Johns Hopkins in 1908. For the first ten years after graduation he worked as a pathologist in New York, Philadelphia, New Orleans, and San Francisco. In 1918, he became associated with the Department of Pediatrics at Washington University and the St. Louis Children's Hospital. Gradually he became interested in clinical work in addition to heading the laboratory services. His studies in diaper dermatitis, syphilis, and leukemia are well known. He was a member of the Society for Experimental Biology and Medicine, and of the American Pediatric Society, serving as president in 1948-1949.

Dr. Reuel A. Benson of New York died August 6, 1956, aged 78. He had been associated with the Flower and Fifth Avenue Hospitals for over fifty years, and from 1938 to 1949 was professor of pediatrics at the New York Medical College. In 1946, he was appointed professor of graduate pediatrics. He established the Wheeler Laboratory for research in pediatrics.

Dr. Robert A. Aldrich, associate professor of pediatrics at the University of Oregon, has been appointed head of the University of Washington School of Medicine's Department of Pediatrics. Dr. Aldrich assumed his new position August 1. He succeeded Dr. Walter B. Seelye, head of the pediatrics department since it was established in 1947, who has retired.

The **Orthopaedic Hospital** and **Rancho Los Amigos Hospital** (respiratory center for poliomyelitis) announce a seminar in Comprehensive Patient Care and Rehabilitation of Selected Neuromuscular Disabilities, Oct. 22 to 26, 1956, open to physicians with an M.D. degree. Application form may be obtained from "Seminar," Orthopaedic Hospital, 2400 S. Flower St., Los Angeles 7, Calif.

The **American Psychosomatic Society** will hold its fourteenth annual meeting at Chalfonte-Haddon Hall in Atlantic City on Saturday and Sunday, May 4 and 5, 1957. The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1956. The time allotted for presentation of each paper will be twenty minutes. Abstracts, in sextuplicate, should be submitted for the Program Committee's consideration to the Chairman, at 551 Madison Ave., New York 22, N. Y.

The Public Health Service's **National Institute of Neurological Diseases and Blindness** has announced that funds are being made available to medical schools to strengthen existing clinical programs in advanced training in the neurological diseases. The purpose is to stimulate the interest of more young physicians and scientists in careers as teachers and investigators. Training grants also are available to basic science departments to expand postdoctoral training programs in the neurological sciences. Further information, together with application forms, may be obtained from the Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Md.

Books

Youth—The Years From Ten to Sixteen. Arnold Gesell, M.D., Frances L. Ilg, M.D., and Louise B. Ames, Ph.D. New York, 1956, Harper and Brothers, 542 pages. Price $5.95.

This book, whose basic theme is the growth of mind and personality, completes the Trilogy which began in 1943 with *Infant and Child in the Culture of Today.* The authors state, "We felt an increasing compulsion to pursue the cycle of development into the teeming teens, using systematic methods of investigation comparable to those applied in the survey of the progressive age levels from birth to ten years."

The data from which "behavior patterns were identified and were codified into longitudinal *growth gradients* to show the sequences and directions of development" were obtained by examining, interviewing, and testing 83 boys and 82 girls. Fifty of these were seen once during these years and 115 were seen on the average a little more than four times. From 60 to 88 were seen at each of the seven age periods. The mean IQ of this group was about 118, and their high economic status is indicated by the fact that 82 per cent fell in classes I and II of the Minnesota Scale of Parental Occupation (U. S. urban average 19.3 per cent). These data are presented in a series of "*Maturity Profiles*" which "portray the maturity characteristics of each yearly age zone regarded as a whole," and in text which discusses over forty "*Maturity Traits*" such as physical growth, sex interests, eating, clothes, anger, self-assertion, wishes, crushes, reading, school, honesty, death, et cetera.

Each of the first ten chapters describes the maturity traits which the authors state characterize the seven successive age zones from 10 to 16. First there is a profile of which the following abstract of that for the Fourteen Year will serve as an example.

"The shyness, the touchiness, and the gingerly vagaries of Thirteen give way to a robust, vigorous expressiveness. There is more laughter and more noise and singing in the house. . . . He has a new self-assurance despite the pressures of a mounting energy. . . . Despite a tendency to feel highly embarrassed by parental conduct, the basic relationship with the family circle has become more genial and less tense. . . . Boys in general prefer boy companions, as friends and as members of an activity group." . . . Then follows a more detailed discussion of each maturity trait. The final nine chapters examine the trends which the data suggest to the authors and develop a thesis that the *sequences* of development show little variability.

The authors readily admit that the group studied is a highly selective one. Commendably they emphasize the dangers in forgetting normal variations in *time* of growth or in confusing the authors' age groups such as "Year Fourteen" (which are developmental stages) with any given adolescent's chronological age. It is fervently to be hoped that anxious parents read and fully understand this and the authors' italics on page 15:

"The maturity profiles, the maturity traits, and the maturity trends are not to be regarded as rigid age norms nor as models. They simply indicate the kinds of behavior—desirable or otherwise—which tend to occur at certain stages and ages under contemporary cultural conditions. Every child has an individual pattern of growth unique to him. The profiles, traits, and trends are designed to suggest the various maturity levels at which he is functioning. The 'ages' denote approximate zones rather than precise moments of time."

This book reiterates the concept that young people's development proceeds according to an over-all pattern and has a plan;

that, for example, there is a trend from dependence to independence over these years. Due perhaps to the size, composition, and nature of the study, the authors' comments seem to this reviewer to underestimate the normal but often striking vacillations (the fits and starts, the advances and regressions) in behavior characteristic of members of this age group, and to minimize—no doubt because such items as bathing, eating and clothes, etc., tend to obscure them—those major and, for many adolescents, disturbing problems arising out of their adjustment to sex, the acquisition of independence, the readjustment of the parental relationships, and their need to achieve success.

J. ROSWELL GALLAGHER

Allergy in Childhood. Jerome Glaser, M.D., American Lecture Series, Springfield, Ill., 1956, Charles C Thomas. Price $12.50.

In a lucid, readable, well-organized, and practical style, Dr. Glaser presents a monograph on *Allergy in Childhood* which should be required reading for all pediatricians, students, and allergists who treat children. Major emphasis is placed on the two principal manifestations of allergy, eczema, and asthma. The differential diagnosis between allergic and seborrheic eczema and other rashes is noteworthy. The features which distinguish asthma from other conditions which cause wheezing in infants and children are described in detail and with enough suitable illustrative case reports to make them vivid. For the nonpediatrician the chapters on certain conditions peculiar to the pediatric age group, such as fibrocystic disease of the pancreas, galactosemia, congenital malformations, congenital lobar emphysema, and the foreign body problem should be invaluable.

The treatment for skin and respiratory symptoms is detailed, practical. Dr. Glaser's own prescriptions, the lists of comparable proprietary products, and his outlines of instructions should help pediatricians to prescribe symptomatic treatment logically. The author's indications, methods, and precautions in using ACTH and cortisone in acute allergic emergencies and in chronic allergic conditions are clearly stated, subject to revision as experience with these drugs and their newer derivatives accumulate. There is a good discussion of the tonsil and adenoid problem and of both allergy and infection of the upper respiratory tract. The so-called minor allergies, or less common forms of allergy such as urticaria, drug and insect allergy, purpura, migraine, neuroallergy, collagen disease, are adequately covered with pertinent current references.

In the controversial aspects of allergy there is a dispassionate presentation of divergent views. Examples of this are seen in the chapters on G.I. allergy, colic, and psychosomatics. A section is devoted to the author's studies on the prophylaxis of allergic disease, among these being to avoid cow's milk feeding in early infancy. This thesis has occasioned much discussion and controversy, but it is presented with no disproportionate emphasis, and with much logic along with many practical observations on immunization, etc., of allergic children.

Dr. Glaser calls attention to one important misprint, on page 335, "as a single dose," should read "per 24 hours," in referring to Benadryl. The book is notable, among recent books on allergy, for containing the essential information regarding pollenosis, allergens, diets, etc., without repetition and padding with theory, standard tables, etc., from other sources.

The major defect in the book is that the reproduction of many of the author's excellent color photographs is poor, and detracts from their usefulness in amplifying the text. It is hoped that when this book is republished this will be corrected.

Contribuição para o Estudo Anatômico dos Nervos da Parede Ventro-Lateral do Abdômen no Recém-nascido de Têrmo. Virgilio Alves de Carvalho Pinto, São Paulo, Brazil, 1955, 149 pages.

A monograph describing the author's study of the innervation of the abdominal walls made on fifty cadavers of newborn infants. The author's studies lead to the conclusion that a transverse incision is preferable for a laparotomy.

Editor's Column

THE VIII PEDIATRIC CONGRESS IN COPENHAGEN

THE VIII International Congress of Pediatries held in Copenhagen, July 22 to 27, is now a matter of history. Without comparative comment on previous meetings it will be remembered as an outstanding success. The planning and organization of the meeting were superb, and the greatest praise is due the Danish Organizing Committee with Professor Plum as Chairman and Dr. Vesterdal the Secretary-General. The various subcommittees on meetings, exhibitions, entertainment, etc., had obviously worked for months on the details and the result was a smooth-running meeting which could not have been improved upon. We express the feeling of all who attended in extending our sincere thanks and congratulations to those who were involved in the planning and organization of the Congress.

Some 1,500 pediatricians from sixty-two countries were registered. Of these, 420 were from the United States, 15 from Canada, and 79 from eleven of the Central and South American countries. The German delegation of 224 was the second largest group. Including wives, children, and others in attendance, some 3,500 descended on Copenhagen for the six days. This naturally created a difficult hotel problem, and it was the general feeling that it had been handled splendidly and in a fair and equitable manner by the local committee.

The Congress was opened Sunday afternoon at the City Hall in Frederiksberg, where Prof. Plum welcomed the members. He was followed by Her Majesty Queen Ingrid, who most graciously welcomed the members to Denmark. That evening a reception was held in the City Hall of Copenhagen, followed by a special Congress-Fireworks display in the near-by Tivoli Gardens.

The Scientific program started Monday morning and continued through Friday afternoon. Plenary sessions were held in the mornings, and in the afternoons as many as eleven Sectional meetings on different topics were taking place at the same time. In all, 393 papers were presented. A 225-page book of abstracts was given to the members on registration. To discuss the individual papers is obviously an impossible task. Sufficient to say there was something to interest everyone, and it was a splendid demonstration of the interest in scientific pediatries throughout the world. Perhaps of even greater interest was the scientific exhibit and the "film hall" which were constantly thronged. There were 143 graphic exhibits of the work being done in the children's clinics of many countries.

The "entertainment" part of the meeting added much to the enjoyment of the Congress. In addition to sightseeing tours and fashion exhibitions for the ladies, special programs for the

A Few Familiar Faces at the Meeting

President Plum
Copenhagen

Davison
Durham, N. C.

Helmholz
Rochester, Minn.

Janeway
Boston

Karelitz and Carl Smith
New York

Gairdner
Cambridge

Farber
Boston

PLUM
Copenhagen

GAMBLE
Boston

JONXIS
Groningen

BARNETT
New York

COE
Seattle

FISCHER
Philadelphia

LEVY
Memphis

NELSON
Philadelphia

CRAIG
Aberdeen

CHRISTOPHERSON
Chicago

SALAZAR
Lisbon

FRONTALI
Rome

AGUIAR
Rio de Janeiro

MASSLOV
Leningrad

VAN CREVELD
Amsterdam

MONCRIEFF
London

STRANSKY
Manila

SCHLESINGER
London

STOKES
Philadelphia

children were included. The social end culminated in the Wednesday night dinner starting at 8 at restaurants in the Tivoli Gardens. At 11:30 a special concert was given in the beautiful new Concert Hall and the Gardens, which were kept open until 2 A.M. for dancing. The Danish Pediatric Society was a most gracious host.

Many from the United States took the "Congress Tours" sponsored by the Academy of Pediatrics. A first group reached England early in July, and after a few days in London took two weeks in Norway and Sweden before reaching Copenhagen. A morning was spent at the Great Ormond Street Hospital in London, and another at the Children's Hospital in Oslo. In Stockholm, clinics were held one morning at the Karolinska Sjukhuset, followed by lunch, and then ward rounds at the Kronprinsessan Lovisas Children's Hospital. In Olso and Stockholm a special dinner was arranged at delightful restaurants. A second, much larger group reached London two weeks later, where a program of clinics was given at Great Ormond Street. One evening the Academy group and the British Pediatric Society had a delightful dinner at the Mansion House arranged by the British pediatricians. Following the Copenhagen meeting many took advantage of tours through various parts of the continent.

While the Scandinavian tour was a most enjoyable experience as a whole, it was marred by the failure of the travel agency officially selected by the Academy to live up to the promises made in the prospectus and sent to Academy members, providing for first-class hotel accommodations. In Stockholm, in particular, the hotel accommodations for over half the party was "third class" (or as one Swedish pediatrician stated, "fourth class") although there were numerous first-class hotels in Stockholm where tours of other travel agencies were being accommodated. How the post-Congress tours fared in this respect is unknown at the time this is written. If in the future a society appoints an "official agency" for tours to other countries, care should be taken to select an agency which will live up to the promises in the prospectus of the tour. Many traveling independently had no difficulty in securing good hotel accommodations.

The IX Congress in 1959 will be held at Montreal, Canada.

INCREASED GOVERNMENT FUNDS FOR MEDICAL RESEARCH

ACCORDING to press reports the sum of $170,400,000 was appropriated at the recent session of Congress to the seven National Institutes of Health for the fiscal year June 30, 1956, to July 1, 1957. This is an increase of 80 per cent over the appropriation for the previous year. Most of the money will be allotted to medical schools, hospitals, clinics, and laboratories engaged in medical research. The sums were considerably in excess of the amounts requested by the Institutes when the January budget requests were submitted. A few examples are as follows.

	Allotted	*Requested*	*Increase over 1955-1956*
Cancer	$48,400,000	$32,400,000	$24,800,000
Heart disease	33,300,000	22,100,000	18,700,000
Mental health	35,100,000	21,700,000	18,000,000
Neurology and blindness	18,600,000	12,100,000	9,800,000

In view of these increased appropriations for medical research, to which everyone contributes through taxes, more than ever the question arises as to the need and desirability of special "Fund-for-a-Disease" campaigns for medical research.